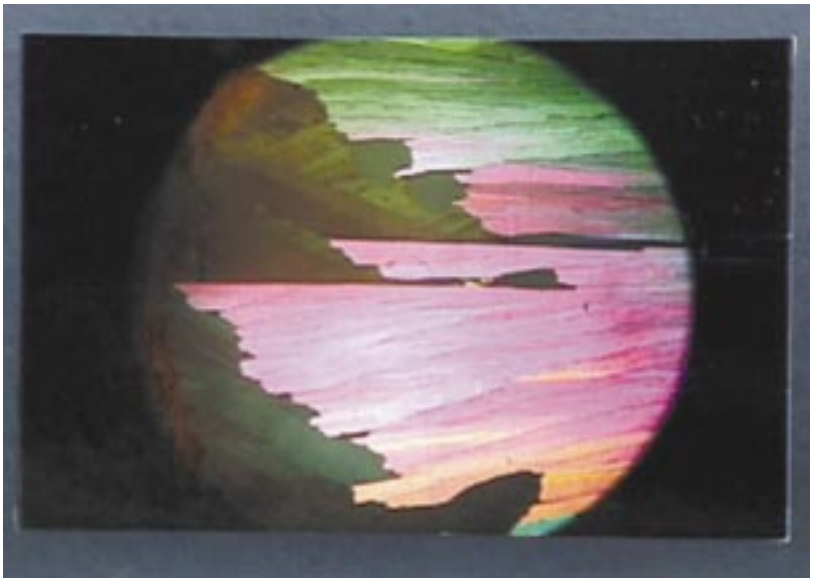
AMERICAN CRYSTALLOGRAPHIC ASSOCIATION
NEWSLETTER

Number 3 ***Fall 2000***

Winners of the Art with Small Molecules Competition

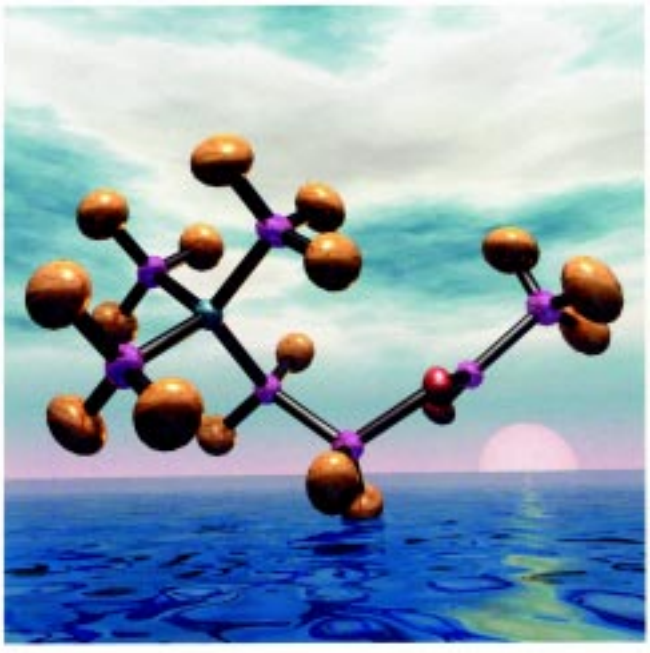


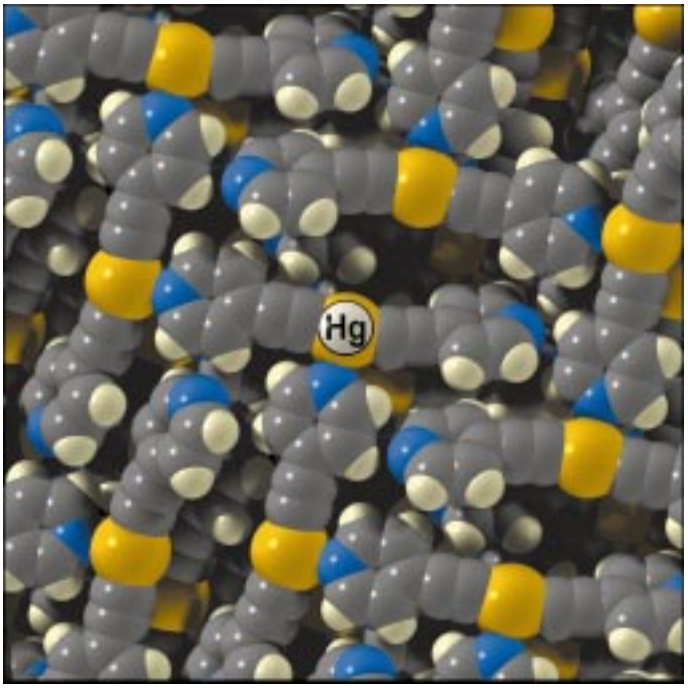
The Seascape

First Place winner by Cecil Simpson

Nanodali *(right)*

Second Place winner by Kenneth Shankland





T-shaped *(left)*

Third Place winner by Joseph W. Lauher

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Articles by e-mail or on diskettes are especially welcome. Deadlines for newsletter contributions are: February 1 (Spring issue), May 1 (Summer), August 1 (Fall), and November 1 (Winter). Matters pertaining to advertisements, membership inquiries, or use of the ACA mailing list should be addressed to:

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ACA Newsletter (ISSN 1958-9945) Number 3, 2000. Published four times per year in the spring, summer, fall and winter for the membership of the American Crystallographic Association, P.O. Box 96, Ellicott Station, Buffalo, NY 14205-0096. Membership in the ACA includes a non-deductible charge of $1.75 from membership dues to be applied to a subscription to the *ACA Newsletter*. PERIODICALS POSTAGE PAID AT BUFFALO, NY. POSTMASTER: Send address changes to ACA, c/o 73 High St., Buffalo, NY, 14203.

President's Column

I regard our recent St. Paul meeting as a huge success. The science presented was terrific, the ambiance was exceptionally good and the social events were a lot of fun. The meeting went very smoothly thanks to the organizational skills of the Local Committee and the Program Committee (Local Chairs Victor Young and Bill Gleason; Program Chair Doug Ohlendorf). The ACA Council is nevertheless concerned because this meeting did not have the attendance it most certainly deserved. (Attendance was about midway between that of the Buffalo and St. Louis meetings, but spring meetings such as Buffalo always have lower attendance.) This naturally translates to money. As I write this we don't yet know the final numbers, but we may need to use some of our reserve funds. This is not a problem if it happens only once in two or three years, but it is a wake-up call. We keep good track of all sorts of statistics, and we will try our best to understand the reasons for the decrease because it is important to the planning of future meetings. We need to know if this is the start of a trend, or can be traced to factors we can hope to correct.

Some suggestions for changing our meeting format came out of Council meetings with SIGs and Standing Committees and other discussions, and it may be that future meetings will try out some of these ideas on an experimental basis. Plenary lectures of broad interest (similar to IUCr meetings) were suggested. Planning symposia farther in advance and with better funding might help, especially if the result is that each meeting has at least one high-powered symposium likely to be a draw. One change already agreed upon is that starting with the 2002 meeting in San Antonio a symposium will be built around the award recipient for the year (Patterson Award in 2002). Another format change under consideration is to try offering excursions at reduced prices immediately following the meeting. This would entail staying an extra night, but might be quite enjoyable. Remember our afternoon outings? Please send us any ideas you have for improving the meetings. To those among you who did not come to St. Paul: too bad, you missed a good meeting, but if your reason is one we should know about, please tell us.

continued on next page

On another front, I have appointed an *ad hoc* Web Advisory Committee with Jeff Deschamps as Chair, John Westbrook, and Jim Fait. They will be working on electronic voting and e-commerce issues first, but will also be available to help evaluate any proposals for upgrading the ACA website that might be received. The Publications/Communications Committee report we received in St. Paul reiterated their intention of developing, categorizing and describing crystallographic education and training sites. This will be done in cooperation with the Crystal Data & Computing Committee. They would very much appreciate receiving information about relevant websites (you can find their addresses under Standing Committees on the ACA website).

The need for better science education can scarcely be overemphasized. This is true in general, but is especially urgent for crystallography as we face the reality of decreased emphasis on formal courses in universities and increased participation from scientists based in other disciplines. Better utilization of the web is a practical way to support this goal, and we should try hard to use our opportunities wisely.

Connie Chidester

Art with Small Molecules Competition

We are pleased to announce that Cecil Simpson's "The Seascape" has won first place in the WOW-2000 Art with Small Molecules Contest sponsored by the Small Molecule SIG of the ACA. The winning artwork is shown on the cover of this issue of the Newsletter.

The winners were announced at a joint dinner of the ACA Small Molecule SIG and the ACA Service Crystallography SIG attended by 60 cheerful and enthusiastic members the evening of 23 July 2000 at the Great Waters Brewery in St. Paul. Dick Harlow judged the event and announced the winners. Since none of the entrants were students, the cash prize will be carried forward to next year's competition. Submissions for the WOW-2001 competition to wow@bernstein-plus-sons.com are encouraged. Helen Berman has agreed to serve as the chief judge for next year's competition. Final rules for the 2001 competition are still to be determined, but the approach is expected to be similar to the relaxed and light-hearted approach used this year. Submissions wil be accepted starting immediately. In order to allow time to organize web pages before the ACA meeting in 2001, the deadline for WOW-2001 submissions is June 30, 2001.

We cannot do justice to the quality and beauty of the winning images on these pages. Full details of the contest and high resolution JPEG images are available via the web at http://www.bernstein-plus-sons.com/wow-2000

The first place entry was a photomicrograph taken at 70X by Cecil Simpson of Lubbock, Texas, with a stereo Olympus microscope using cross polarization. The resulting "birefringent" crystals were obtained using small quantities of 9-fluorenone mixed together on a microscope slide and melted using an alcohol lamp. A cover glass was placed on the clear liquid and the material allowed to cool at room temperature. The resulting crystals were then photographed. Non-birefringent crystals do not produce colored crystals.

If you are interested in purchasing an 8 x 10 or 16 x 20 image from Cecil Simpson, please contact him by email at CTSchess@aol.com.

The second place entry, "Nanodali", was a POVRAY drawing of acetylcholine rendered by Alastair Florence of Glasgow, Scotland and submitted by Kenneth Shankland of Chilton.

The third place entry, "T-shaped" was a Chem-Ray drawing submitted by Joseph W. Lauher of Stony Brook showing the crystal packing of Mercury(II) bis(4-pyridylacetylide) from a structure determined by Lauher's graduate student Sean Curtis.

If you have any questions about this year's competition or about the WOW-2001 competition, send email to wow@bernstein-plus-sons.com.

Herbert J. Bernstein

New Member of the National Academy of Sciences and New AAAS Fellows

Doug Rees was recently elected to the National Academy of Sciences, and Joel Bernstein, Michael Rossmann and Jenny Glusker were elected fellows of the American Association for the Advancement of Science.

K.C. Cole to Receive the Elizabeth Wood Award

K.C. Cole, a science writer for the Los Angeles Times, will receive the ACA's Elizabeth Wood Award at the 2001 meeting. This is in recognition of her writing about science for the public. Her columns run about twice a month in the LA Times, and you can see her latest at the website www.latimes.com She wrote "The Universe and the Teacup" which covers mathematics-for-the-layman and "First You Build A Cloud", an earlier book describing elements of physics. She has also received the AIP Science Writer of the Year Award. She will give a presentation at the annual banquet in Los Angeles.

Compton Award Given by the APS

Donald H. Bilderback, Andreas Freund, Gordon Knapp, and Dennix Mills have received the 1998 Compton Award from the Advanced Photon Source (APS) at Argonne National Laboratory. They were cited "for their innovation and leadership in developing cryogenically cooled X-ray optics suitable for handling the high power density of undulator X-ray beams, thus allowing users to perform scientific research at the third-generation synchrotron facilities." The award was established by the APS Users Organization to recognize an important technical or scientific advance beneficial to the APS.

First European Crystallography Prize Awarded to Professor Ada Yonath

The European Crystallographic Association awarded the first European Crystallography Prize to Professor Ada Yonath of the Weizmann Institute of Science Rehovoth, Israel and the Max-Planck Research Unit for Ribosomal Research, DESY, Hamburg, Germany. Professor Yonath is being recognized for her pioneering achievements in structural studies on the ribosome, the universal cellular organelle on which protein biosynthesis takes place.

The European Crystallography Prize, which includes a monetary award as well as a certificate of recognition, was presented at the 19th European Crystallography Meeting held in Nancy, France, August 25-31, at which Professor Yonath described the work for which she has been honored.

Members of the Prize Committee, who were appointed by the Executive Committee of the European Crystallographic Association, are Prof. Michael Hursthouse (Univ. of Southampton, UK), Prof. Neil Isaacs (Univ. of Glasgow, UK), Prof. Jan Kroon (Univ. of Utrecht, The Netherlands), Prof. Carlo Mealli (ISSECC-CNR, Florence, Italy), and Prof. Eric Mittemeijer (Max Planck Institute for Metals Research and Univ. of Stuttgart, Germany). The Committee was chaired by Prof. Joel Bernstein (Ben-Gurion University of the Negev, Beer Sheva, Israel).

Professor Yonath was born in Jerusalem and received her Ph.D. under the direction of Prof. Wolfie Traub at the Weizmann Institute, where she is the incumbent of the Martin A. Kimmel Chair in Structural Biology and Head of the Kimmelman Center for Biomolecular Assemblies. Her pioneering work over many years in pursuit of the ribosome structure, which she has orchestrated on an international scale, has been concentrated in Europe, with a significant portion of her activity centered at the Max-Planck Research Unit in Hamburg, which she also heads.

The European Crystallography Prize is sponsored by Bruker Analytical X-ray, Karlsruhe, Germany, STOE & CIE GmbH, Darmstadt, Germany and Philips Analytical B.V., Almelo, The Netherlands.

Joel Bernstein

ICDD International Sales Manager

The ICDD welcomes Mr. Dominique Pfeffer as their new International Marketing Manager. Dominique brings a wealth of knowledge about the global market with him. He has 20 years of experience in international business, from banking in Europe and the U.S. to manufacturing, sales and marketing.

His interests range from human welfare to history. He is a member of the Philadelphia Breakfast Club and Habitat for Humanity and also serves as a member of the Civil War Institute. Dominique loves sailing and is an extreme soccer fan. Dominique recommends that you avoid discussing soccer with him if you are in a hurry!

Helen M. McDonnell

The Structural Molecular Biology Synchrotron Radiation Enterprise: An Interagency Partnership

In the past decade, synchrotron radiation (SR) based structural molecular biology (SMB) has undergone a remarkable evolution [1]. The availability of reliable and sustainable access to synchrotron beams, coupled with advances in X-ray optics, detectors, computational power and software, have transformed SR-based SMB experiments from being a heroic effort in the 1980s to a technique with great breadth and depth across a wide range of basic and applied biomedical sciences. The organizations that fund the operation of the synchrotrons, the DOE Office of Basic Energy Sciences (BES) and the National Science Foundation (NSF), have made this growth possible because they ensured that the facilities were open to all disciplines based on scientific merit. Although these facilities were justified, built and operated primarily for condensed matter physics, I can say, based on my personal experience, that these organizations have also nurtured and encouraged the use of SR for non-traditional applications, including SMB, during the early years when new techniques were being developed. Much of the growth in demand has been driven by macromolecular X-ray crystallography for which most published results now depend on synchrotron radiation. In 1998 40% of new structures published used SR compared with only 18% five years earlier [2]. For 1999, this number has increased to ~57%. The use of multiple wavelength SR (called MAD) to solve the classic phase problem in crystallography, especially when coupled with site-specific substitution of methionine by selenomethionine to provide a specific X-ray "tag", now enables macromolecular structures often to be solved in matters of hours rather than many days or even months as was common a decade ago.

The extremely high intensity and collimation of SR have allowed access to a much wider range of large and complex biomolecular structures with resolutions that can approach individual atoms. Complementary biophysical techniques using SR, including small angle X-ray scattering, X-ray absorption spectroscopy, and X-ray microscopy, and similar techniques in the vacuum ultraviolet and infrared regions also provide new windows on studying problems, including protein folding, metal ion active site structure, and cellular organization. It is interesting to consider just why and how this enterprise has come to be and what the prospects are for the future. While vigorous growth in SR-based SMB is being seen worldwide, and indeed is one of the primary drivers for the construction of new synchrotrons in the United Kingdom and elsewhere, I will focus these brief remarks on the activities in the U.S. synchrotron sources that produce high intensities of X-rays. They are relatively costly to build ($100-700M range) and operate ($10M to $100M/yr). However, since the sources typically run year-round and serve many users simultaneously, the effective operating costs per user are only in the few hundred $/hour range. Fortunately, access to the U.S. facilities is based primarily on quality of science, as judged by competitive peer-review, and not on factors like ability to pay for beam time since the base operating budgets of all the major U.S. facilities are being

provided by governmental agencies. Indeed, every synchrotron facility serves a substantial number of general users through a peer-reviewed proposal system. This insures an opportunity for all structural biologists to gain access to these facilities, regardless of institutional affiliation or source of research funding.

In the U.S. there are five major synchrotron user facilities (four operated by DOE and one by NSF) that serve the hard X-ray region. Collectively, they accommodated about 6000 academic, national laboratory and industrial users in FY1999 of which about 1/3 (2000) are working in the life sciences area (with the largest single fraction being in macromolecular crystallography). A decade ago, the number of life science users was only a few hundred. To carry out structural biology at the synchrotrons also requires specialized resources including beam line scientists and support staff who train users and keep the beam lines functioning in an efficient and user-friendly fashion, advanced detectors and computing. Such an individual facility (or beam line) costs typically $4-10M to build and $0.5- 1.0M/ year to operate. Funding for the U.S. SMB beam lines has until recently come primarily from federal sources including the DOE Office of Biological and Environmental Research (DOE-BER) and the National Institutes of Health, National Center for Research Resources (NIH-NCRR). There had also been investment by private enterprise, including the Howard Hughes Medical Institute and industry. Building and sustaining this infrastructure for SR-based SMB research and user support has come as a result of a partnership between the agencies that operate the synchrotrons (DOE Office of Basic Energy Sciences [DOE-BES] or NSF) and those supporting the beam lines. Recently, the National Institutes of Health Institute for General Medical Sciences (NIGMS) has also begun to help support elements of beam line operations and instrumentation improvements for macromolecular crystallography that leverages greatly the ongoing support of DOE-BER and NIH-NCRR. In the case of two of the DOE-BES operated synchrotrons, NIH has recently partnered with DOE to enable important upgrades in the capabilities of the machines themselves. The partnering between the agencies was facilitated by the Office of Science and Technology Policy (OSTP) when it established an interagency working group (chaired by Marvin Cassman of NIGMS) to coordinate government agency activity and funding in responding to needs in this expanding area [3].

As one looks toward the future, initiatives like that from NIGMS in structural genomics, from DOE-BER in microbial cell research, and from NCI in targeted drug design will drive demand for SR at an increasingly rapid rate. This will add to the growing utilization of structural information on biomolecules in areas from understanding cell signaling and immunology to structure-based drug design and molecular medicine. It is very important for the user community (and bodies that represent it like the Biophysical Society (and the ACA. Ed. note)) to recognize and support the unique partnership among the federal agencies that has evolved to enable this enterprise to develop. Without construction and operations funding from DOE-BES and NSF or without the specialized capabilities provided primarily by DOE-BER and NIH it would not be. A strong case for interagency partnership is made in a recent National Academy report [4]. All too often, the tendency is to see the synchrotron as a "filling station" (albeit a sophisticated one) without acknowledging the large effort and financial commitment required to maintain highly reliable operations, state-of-the-art instrumentation and user support. As users, we need to lend our support to maintaining growth in the base budgets of DOE-BES, DOE-BER, NIH and NSF. The FY2001 Federal budget includes increased funding for the SR facilities, for research and for new facilities (see for example the FASEB report on Federal Funding for Biomedical Research [5]). One of the new facilities under construction is the Spallation Neutron Source (SNS), which will provide unparalleled opportunities for neutron-based investigations that are very complementary to studies by X-rays; another facility in an R&D phase is a fourth generation synchrotron X-ray light source. DOE and NSF have been effective stewards of our national SR user facilities and their continued support and growth will be a crucial factor to provide the means for us to carry out our research in this era of remarkable discovery in the biological and biomedical sciences.

References:

1. Special issue on SMB of *J. Synch. Rad*., 6 (part 4), pp. 809-944, July, 1, 1999.

2. For an account of growth up to 1997, see the *BioSync Report* at http://www.ornl.gov/hgmis/biosync/

3. OSTP report *Synchrotron Radiation for Macromolecular Crystallography* at http://www. whitehouse. gov/WJ/ EOP/ OSTP/Science/html/ cassman_rpt. html.

4. *Cooperative Stewardship: Managing the Nation's Multidisciplinary User Facilities for Research with Synchrotron Radiation, Neutrons, and High Magnetic Fields*, National Academy Press, 1999.

5. See http://www.faseb.org/opar/fy2001/ biofy2001.pdf

Keith O. Hodgson

(Reprinted from the Biophysical Society March 2000 Newsletter.)

Additional Comments on the History of the ACA

Our 50th Anniversary isn't over yet. Stories and comments on the development of crystallography and the ACA can still be submitted for a special edition of the Newsletter containing the comments of past-presidents and other early members of the organization. Here are comments from David Templeton, Clara Brink Shoemaker and Tom Furnas that were not included in the previous issue.

David Templeton (ACA President - 1984)

When I was President in 1984, with a Congress in Hamburg, the only ACA meeting was in Lexington in May. A high point for me was the pleasure of presenting the Patterson Award to Jerry Karle and Herb Hauptman. A less enjoyable memory (probably shared with other officers before and since) was the many hours in administrative meetings which conflicted with scientific sessions. One unsuccessful project that year was an early attempt to submit abstracts by electronic means. For example, the character which signified "subscript" at the Institute of Physics was the signal for "delete line" on the terminals used at some other locations. A perennial problem was laggard authors of papers for the Transactions. Another was poor communication with the Institute of Physics, where our only employee generally worked for us only one day a week. Much of the work involved plans for future meetings. The decision was made to go to only one meeting a year instead of the previous practice of two in non-congress years. A revelation for me was to learn how much ACA is in debt to a dozen or so members whose work over the years, with little public recognition, kept the organization going.

In my memories the ACA really started with ASXRED and the 1949 meeting at Cornell University. The transition to ACA the next year was invisible to me because the character of the meetings hardly changed and so many of the participants were the same people. The meetings then were smaller, with no parallel sessions. As a new member, with barely two years experience in crystallography, I was scheduled as the third paper in the opening session, at 7:00 AM California time, after another young man, Bill Lipscomb. I do not know how I woke up that early. I arrived, the evening before, exhausted and air sick after a trip of 24 hours on a succession of unpressurized DC-3 planes which flew over the Sierra Nevada and the Rocky Mountains and through several mid-western thunderstorms. Travel is much easier now. The first crystallographer I met in the dorm was Lindo Patterson, who introduced himself and welcomed me to the meeting. A box lunch on the lawn was a predecessor for the picnic of later meetings. As I sat on the grass I was joined by Linus Pauling, who quizzed me about what I was doing and what was going on in Berkeley. There was no need at that time for organizing a Young Scientist Mixer.

David Templeton

Clara Brink Shoemaker (DavidShoemaker ACA President - 1970)

To the ACA at its 50th Anniversary Celebration:

My congratulations to the ACA at its Golden Anniversary!

Although I was not present at the first meeting of the ACA at Penn. State College, I had entered the world of crystallography in that same year by getting my Ph.D. in Holland on the structural determination of compounds so simple that I don't dare to mention them.

My memories of the ACA go back to 1953 when I came to the USA, and then in 1955, married David Shoemaker. The ACA became an important part of our lives with David serving as member of the USA National Committee for Crystallography, president of the ACA, chairman of the 8th International Congress of the IUCr in Stony Brook, N.Y., member of the Executive Committee of the IUCr and co-editor of Acta Crystallographica.

I remember the early meetings of the ACA with fierce fights about the feasibility of Direct Methods. And, as David remembered in his contributions to the "Crystallography in North America (1983)", there were also fights on the international scene about non-democratic tendencies in the International Union. Through it all, the ACA bound its members together and friendships for life were formed.

The ACA is different now with many more members and with the emphasis of research shifted to biological compounds, getting incredibly beautiful results, that would have astonished the early pioneers in the field!

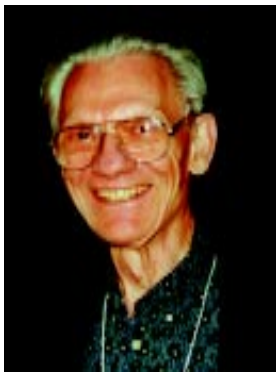
My wish is that the ACA will continue to play an important role in the lives of its members!

Clara Brink Shoemaker

Future crystallographers comparing notes at the Opening Reception in St. Paul

Thomas Furnas

Fifty Years of Memories with ACA



In the summer of 1950, while finishing my Ph.D. research at MIT, (Professors Bert Warren, Martin Buerger and Richard Bear were my Advisors) involving focusing X-ray cameras & their application to the study of collagen, etc., I heard of David Harker and his proposed establishment of a Protein Structure Project. I was excited and very interested, wrote a letter to David Harker, was invited to Schenectady, was present when word was received from IBM that the Project was promised any and all computing facilities that may be required (with others of the staff, we toasted the "birth of the Project" with MILK). I was offered and accepted a position on that Protein Structure Project to design the new equipment that would be required. This position was the culmination of my interests, dreams and deliberate training since I was in high school.

Also in 1950, I biked from Cambridge to New Hampton, N.H. to attend the second meeting of the American Crystallographic Association. It was an awe inspiring experience. I continued to attend every ACA and IUCr meeting until the 1971 meeting in Ames, Iowa where I suffered a back injury which changed my life.

Dave Harker's initial idea for automatic data collection was based upon the precession camera geometry using charts with linkages to scan them and relay the information by servo to a diffractometer and counter electronics. I found that an impossible situation and proposed a drastically different approach which Dave recognized as the Eulerian geometry, and his principal contribution regarding the instrumentation was not only to name it but also to give me total freedom and encouragement to pursue it. I made drawings & clay models which our instrument maker, Bridgy Weber, was wonderful at being able to convert into metal. We were a great team and I very much appreciated the opportunity to work with him. It also was an extraordinary experience to be at Brooklyn Polytech where the world's crystallographers always stopped on their way in or out of the USA.

In 1954, Dave Harker returned from a GE training school with the description of a prototype of a new device which GE was preparing to manufacture for the diffractometric collection of data. It was based upon the normal incidence Weissenberg geometry. I told David Harker "That was a terrible thing to foister upon the unsuspecting crystallographer". While on the Long Island Railroad going home that evening, I decide that it had to be stopped, so I set out to design the GE Single Crystal Orienter. David Harker concurred the next day and during that one week before the ACA Meeting in Boston, I did just that. We sent a set of the drawings special delivery to Howard Pickett of GE in Milwaukee and brought a set to the Boston ACA Meeting. We gave the GE people not one minute of rest during that ACA meeting. As chairman of the ACA Apparatus & Standards Committee, I called a special meeting to bring attention to the fact that automatic diffractometers were going to be a big part of the future of crystallograhy and that there was immediate need to standardize goniometer heads. Martin Buerger, Bert Warren and many others stood and voiced strong agreement. Bill Parrish countered that there were already as many goniometer heads in existence as were needed so it was unnecessarry. Fortunately he later seemed to have a change of heart as the IUCR Apparatus & Standards committee (of which he was a member) did finally approve and adopt standards.

The GE Single Crystal Orienter design played a unique role in those standards as the 4.000" height of the X-ray beam above their Spectrogoniometer table was not enough space for the original 63.96 mm height when the required omega motion was inserted into the base. Therefore, and also to satisfy our European friends, I proposed an alternative 49.00 mm height if it were a eucentric goniometer head (i.e. the arcs must have a common intersection of their axes and the translations above the arcs).

A less successful project concerned the standardization of camera tracks to a dovetail design which would permit secure, reversible and reproducible positioning and also be independent of gravity. Although accepted by the ACA, it was rejected by the IUCr. However has become a very widely used design in laser instrumentation.

1954 also was a very exciting year for me as I was able to attend the IUCr meeting in Paris. Enroute I delivered a suit of clothes from Prof Fankuchen to Professor Bernal in London, was invited to give lectures on Focussing Monochromators and/or Single Crystal Instrumentation to groups headed by Professor DeWolf and by Professor Bouman in Delft (where I bought a bicycle for the remainder of my travels), Professor Bijvoet in Utrecht, Professor MacGillavry in Amsterdam, and separately to groups with Professors Couchois and Guinier in Paris. I was invited to return to London and made presentations for Professor K. Lonsdale and her group, for Professor Wilkins and his group, then off to a presentation at the Cavendish in Cambridge. A hurried train trip back to London where my bicycle and I were put up at The Browns Hotel by Hilger & Watts who were interested in single crystal instrumentation . While visiting Dr. Carlisle's lab, we were interrupted by a hurried exclamation from Professor Bernal that Sir Lawrence Bragg had called and requested that I immediately come to the Royal Institution to tell him about the single crystal instrumentation that I had been describing. Dr. Uli Arndt also was present at that meeting.

In 1958 I was given the opportunity by Picker X-ray Corp. to lead a team to bring out a totally new line of X-ray diffraction equipment. We established a Research Center with a complete research applications laboratory. In 1967 we announced and demonstrated at the ACA meeting in Atlanta the first US built commercially available computer

controlled single crystal X-ray diffraction system which became known as the FACS I System.

After my term as chairman of the Apparatus & Standards Committee, I was elected to succeed Professor Jeffrey as Treasurer of the ACA. Our membership passed the 1000 mark during my three and one-half year term (the fiscal year was changed from 1 January to 1 July). I was succeeded by Dr. Ben Post. The Suffern, NY ACA meeting was the first one in which the presentations were tape recorded. I had requested and insisted upon the recordings and I believe that it was Joel Bernstein and others from Bell Laboratories whom we have to thank for bringing it about. This is how our excellent series of Transactions came into being.

The ACA has been a very exciting part of my life. I have enjoyed the many people whom I have met and worked with. I have been a contributor to its well being and advancement, am happy to have had the many opportunities that it has provided to me and to those who have become its members. I am pleased to continue to contribute new, exciting instrumentation and accessories through Molecular Data Corporation.

Thomas C. Furnas

Notes of a Protein Crystallographer

FRODO, The Electronic Hobbit*

From early childhood, John Ronald Reuel Tolkien (J.R.R. Tolkien: 1892-1973) was fascinated with languages. When he was five, his mother - who was fluent in Latin, French, and German- taught him to read in all three languages plus her native English. Fatherless since 1896, the family lived in a small rented cottage in the hamlet of Sarehole by the Cole River, far from the smokestacks and soot of Birmingham. The quiet meadows and streams of Sarehole were a haven for Ronald and his younger brother Hilary. There his mother introduced them to botany and inspired in them a love for plants, trees and the beauty of natural landscapes. Nonetheless, change again came to his life abruptly. His mother died in 1904 and the brothers were left under the guardianship of a Catholic priest, Father Francis Morgan, who had a tremendous influence on his education and his life. Tolkien graduated from King Edward's VI school in Birmingham and won an award to attend Oxford University. His interest and passion for languages led him to study philology, specializing in the literary and linguistic tradition of the English West Midlands with extensive knowledge of Anglo-Saxon (or Old English as in Beowulf), Middle English (the language of Chaucer), and Finnish, Icelandic, Norse and Germanic mythologies and folklore. He was Professor of Anglo-Saxon at Oxford and a Fellow of Pembroke College from 1925 to 1945, and was a Professor of English Language and Literature and a Fellow of Merton College from 1945 until his retirement in 1959.

It is impossible to separate Tolkien's academic achievements from his creation of two multifaceted, highly imaginative, epic stories which had a tremendous influence on the youth of the 1960s all over the world and whose effect still reverberates today. In 1937 he published The Hobbit (1), which received high acclaim as a fascinating children's story in which he introduced as main characters a 'hobbit' named Bilbo Baggins and a magician of sorts named Gandalf. Tolkien later wrote that the origin of the word hobbit seems to be: 'a worn-down form of a word preserved more fully in the language of Rohan: holbyta or 'hole-' (2).

What is a hobbit? In his own words:

' [..] They are (or were) a little people, about half our height, and smaller than the bearded dwarves. Hobbits have no beards. There is little or no magic about them, except the ordinary everyday sort which helps them to disappear quietly and quickly when large stupid folk like you and me come blundering along, making a noise like elephants which they can hear a mile off. They are inclined to be fat in the stomach; they dress in bright colors (chiefly green and yellow); wear no shoes, because their feet grow natural leathery soles and thick warm brown hair like the stuff on their heads (which is curly); have long clever brown fingers, good-natured faces, and laugh deep fruity laughs (especially after dinner, which they have twice a day when they can get it. Now you know enough to go on with'(3)

The illusion of hobbits as calm, simple, people capable of heroic feats caught on quickly and Tolkien was asked to write more adventures of Bilbo Baggins. The Hobbit had ended with Bilbo keeping a ring that he had found during his fight with Gollum, and living happily in the Shire: the idyllic part of Middle-earth where the hobbits lived and that scholars have related to the Sarehole of Tolkien's childhood (4). The author had no desire to write a sequel. Instead, The Fellowship of the Ring, the first volume of the epic trilogy The Lord of the Rings was published in 1954. Soon after, the next two volumes appeared: The Two Towers and The Return of the King. The completed work was a mythological world of monumental proportions in which Tolkien had given life to creatures, kingdoms, wars, calendars, climates, places, landscapes, and seasons to give flesh and blood to the languages spoken by the people of Middle-earth: humans, elves, trolls, goblins, giants, dragons, ents, balrogs, orcs. The hero was Frodo, heir and nephew of Bilbo Baggins, who together with his friend Sam and other companions of the fellowship undertake a quest to destroy the master evil ring of Sauron that Frodo had inherited from his uncle. The appeal of an innocent, gentle creature succeeding in destroying the forces of evil against all odds, in an unspoiled landscape of pristine forests, mountains and lakes was enormous. By 1967, The Lord of the Rings had been translated into nine languages with an estimated readership of fifty million people. The graffito: FRODO lives! (5), appeared in the New York subway as testimony to a cultural phenomenon that had opened a magic wonderland of places, characters and events unhindered by the prosaic incidents of our every day lives. Tolkien had transcended the arcana of scholarly research in obscure languages to create a universal allegory of the constant struggle of good against evil, with strong environmental overtones.

FRODO, the electronic hobbit, had its origins in 1976. Whether the younger generations believe or not, at that time all protein models were built starting from a C_a tracing obtained from markings on an electron density map drawn on small plexiglas sheets stacked up as 'mini-maps' (6). From these guide coordinates, detailed atomic models were built at a much larger scale on a Richards optical comparator known in the trade as 'Richards Box' or 'Richards Folly' using Kendrew model parts (7). Glass or plastic windows had to be drawn by hand with tracings of the electron density contours at the appropriate scale (2 cm=1 Angstrom). Atomic coordinates were laboriously extracted from these wire models by tedious and often inaccurate protocols (8). There was an immediate need for a computerized method that would allow the fitting of an atomic model to the experimental electron density map, and which would remove the tedium and inaccuracies from macromolecular structure determination and refinement.

The idea was floating in the community and several laboratories had initiated projects to achieve that goal. Drs. J. Gassman and R. Huber found a bright young Welsh computer scientist (T. A. Jones) who was interested in living in Munich to develop such a tool, and encouraged him to make it a program useful for the routine operation in a protein crystallography laboratory. Tradition has it that the original program sent data back and forth between a PDP11 and a SIEMENS4004, in a computing environment where many of the programs were named after different hobbits. It was only natural that the central program would be named after the most famous of all the hobbits in Tolkien's trilogy. For obvious reasons, the test version used most of the computing cycles and was called initially SAURON.

As a computer graphics program, FRODO made his appearance in the protein crystallography community over twenty years ago in 1978 (9). As for myself, I got to know FRODO very well in 1981 during three beautiful weeks of immersion during the incomparable Swedish spring. Our friendship developed during many nocturnal model-building sessions at the old Wallenberg Laboratory next to the ancient city castle in Uppsala. I must confess that we had our crises, but he was certainly a very friendly hobbit. I was the one to blame for every crisis. Quite often, I failed to understand his prompts or suggestions, and many times his cues made no sense to me. He was always patient, effective and obedient.

You could CHAT (10) with him via a keyboard but the most effective way to communicate was with a tablet and a pen which would allow you to pick and identify atoms, and select different commands from a MENU on the screen. Obedient to the GO command, FRODO would display for you a certain volume of electron density and using well designed commands you could tell him to BREAK certain bonds and cut the protein chain into pieces. These pieces could then be moved with six degrees of freedom (FBRT) to make them fit into the three-dimensional electron density maps which could be rotated at will with dials or joysticks.

FRODO did not know any protein chemistry, or if he did, he would not explicitly tell you so. It was you who would organize those constellations of points in space into a meaningful protein chain by using the REFInement command. He would faithfully apply the rules of chemistry to certain ZONEs of your spatial points which were covered by your electron density contours. This was a tremendous help when trying to fit those old electron density maps. FRODO was also very handy at modeling exercises by allowing you to create MOLecular objects that you could use either as background while fitting electron density or as objects of study in their own right.

For some time, the rumor (joke) floated in the community that the only documentation for FRODO was "The Lord of the Rings". This might have been true, but in his own humble way FRODO proved to be a very useful hobbit and was the ancestor of many other electronic hobbits that are now well settled in our computer underworld. In addition, his faithful friend SAM was always available to insert or delete residues, create a sequence and do all the necessary bookkeeping so that in the end everything was SAVEd in the disk with "amazing speed" and accuracy. During my visit, FRODO lived in a simple VAX750 computer and his commands were translated into a Vector General VG3400. Later he lived inside many other boxes or hobbit-holes in many other countries. His performance improved as his electronic eyes and hands improved, permitting us to view unimaginable shapes and forms and to examine atomic continents, islands and landscapes of indescribable complexity and beauty. Following his original insights, we can now see atomic crevasses and caves, canyons, rivers, mountain ridges and valleys in different and vivid colors, and subtle hues and shades. FRODO opened for us an atomic underworld that was beyond our reach before. He introduced us to an atomic Middle-world that we could not have imagined without his assistance and that we are just beginning to explore, appreciate and understand.

One could argue that there are no malicious villains in our atomic Middle-world: no Dark Riders or Ringwraiths trying to prevent FRODO from destroying the evil ring. Yet, we routinely encounter, examine, and study molecules with pathogenic and curative properties in our crystals, and a major part of our time is spent trying to understand their interactions with themselves and with others. We are trying to defeat the evil forces of disease, pain and deformity and our operational domain is the atomic Middle-world that FRODO unveiled for us. There are parts of these atomic creatures that we cannot see or cannot fit well in our electron density maps, and that chase us in our sleep like the Dark Riders chased after FRODO and his friends. However, our true Gollum, Shelob and Sauron are uncertainty, lack of knowledge and especially bias and disorder. Those restrictive forces will always be with us. In the meantime, FRODO will live on in the heart of those of us who -once upon a time- built protein models using mechanical parts and read the coordinates of our structures using a two-dimensional grid and a plumb line. He did so many things for us; he was such good a friend....

*Slighted revised from the version published in the PDB Newsletter.

Notes

(1) *The Hobbitt*. J.R.R. Tolkien (1994) 2nd Edition. Illustrated by M. Hague. Houghton Mifflin Company. New York.
(2) *The Lord of the Rings Trilogy*. J.R.R.Tolkien. Part Three: The Return of the Ring. Appendix F.
(3) *The Hobbit*. J. R. R. Tolkien (1994) pg. 3.
(4) Myth Maker: J. R.R. Tolkien by A. E. Neimark. Harcourt Brace & Co. New York, 1996. pgs. 85-86.
(5) *The Lord of the Rings Trilogy*. J.R.R.Tolkien. Part one: The Fellowship of the Ring. Authorized edition of the fantasy classic by Ballantine Books, Introduction by Peter Beagle. (1993). Foreword by J.R.R. Tolkien.
(6) T.A. Jones (1985) *Methods in Enzymology* 115, 157-171.
(7) F. M. Richards (1985) *Methods in Enzymology* 115,145-154.
(8) F. R. Salemme (1985) *Methods in Enzymology* 115, 154-156.
(9) T. A. Jones (1978) *J. Appl. Cryst*. 11, 268.
(10) Actual FRODO commands are in bold capital letters.

Cele Abad-Zapatero

Keith Watenpaugh and His "Retirement" Quilt

Keith Watenpaugh recently retired from Pharmacia in Kalamazoo, Michigan. On the occasion of his retirement party he received one benefit that was a complete surprise. Working from crystallographic depictions of many of the structures Keith has been involved with during his long career, his wife Joyce fashioned this amazing piecework quilt. It is so accurately done that the other crystallographers in the department could easily identify the structures. Keith and Joyce have moved to the state of Washington where they are currently building their dream home on Whidbey Island, which is accessible from Seattle by ferry or causeway.

ACA 2000

St. Paul is the hometown of Charles Schultz, and 75 Snoopy statues clothed and decorated by various authors now stand on its streets.

Bill Gleason, Local Co-Chair

Vic Young, Local Co-Chair

Doug Ohlendorf, Program Chair

The ACA enjoyed a week full of events at its Annual Meeting in St. Paul, July 22-27, 2000. The local arrangements, overseen by Bill Gleason and Vic Young were superb. The Science Center overlooking the Mississippi was a wonderful site for the opening reception, the RiverCentre is a very well-planned and built conference facility, and the rain storm arranged for the river excursion was impressive.

The program organized by Doug Ohlendorf (Program Chair) was highlighted by two special scientific sessions. One was the *Transactions Symposium: Using Crystallography to Understand Enzyme Mechanism*. 12 speakers covered current ideas and questions concerning enzymes in a day-long session. Another major session, *HHMI contributions to Macromolecular Science*, was organized by the late Paul Sigler and chaired by Tom Steitz. 12 HHMI investigators described their research using structural methods to understand biological processes ranging from drug discovery to the structure of the ribosome.

The ACA gave several awards at this meeting, Lyle Jensen received the Buerger Award and Ian Robinson was given the Warren Award. Bill Duax was recognized for his service to the ACA with a special award. Newsletter Editors, Judy Flippen Anderson and Ron Stenkamp, also received ACA Service Awards. Purnell Choppin, President Emeritus of the Howard Hughes Medical Institute, was presented with the ACA's Public Service Award.

Memorial sessions for George Jeffrey and Paul Sigler were also held and were well attended.

Hot Structure Session, 02.01

Chair: Cele Abad-Zapatero

The talks presented at this session were selected from the abstracts submitted specifically for this session and also from the macromolecular structures submitted to other sessions of the meeting. Selection was based on providing the audience with as wide a selection of biological systems as possible in view of the fact that what is 'hot' for some may only be 'lukewarm' or even plain cold for others. Thus the session attempted to give a balanced view of what was novel, intriguing, unique and interesting. In addition, a brief extension of the session at the end allowed the presentation of two brief talks on some of the most recent structures. The session was run on very tight time table but the speakers did their best to accommodate the time constraints; the chair is very grateful for this. Details of several of the talks can be found in recent published papers or others soon to appear. This summary will only mention the highlights of the presentations.

The talks were selected from eight broad categories in the following order, corresponding to the schedule of speakers: 1) genomics/proteomics (K. Lim); 2) structures of therapeutic interests (E. Skrzypczak-Jankum and M. Rao); 3) receptors/ligand complexes (J. Boyington); 4) technological innovation (F. Schubot); 5) G-coupled receptors/receptors control (F. van Den Akker); 6) novel functional characteristics (S. Greasley); 7) large aggregates (J. Harp); 8) last minute additions (redox complex, J. Zhang and bovine Rhodopsin, R. Stenkamp).

K. Lim reported on the novel structures of two genes of *Hemophilus influenzae*: i) HI319, a methyl transferase closely related to catechol-O-methyl transferase but of unknown specificity, possibly His or Met; ii) HI0670, a 144 residue protein which has a novel fold but is of still unknown function. E. Skrzypczak-Jankum discussed the difficulties of working with the short-lived, radiation-sensitive 'purple' lypoxygenase. Nonetheless, she was able to structurally characterize three peroxide complexes at ~2.0 Å resolution using conventional sources. She discussed intriguing chemical details of these complexes. M. Rao described the structure of Glucose-6-phosphate isomerase, the second enzyme in the glycolytic pathway from the thermophylic bacteria *B. stearothermophilus* at 1.93 Å resolution and its complex with D-erythrose-4-phosphate. The complex allowed him to identify specific residues as strong candidates for the catalytic mechanism. J. Boyington presented the recently published (*Nature* 405, 537-543 (2000)) structure of an NK cell receptor bound to its class I MHC ligand (KIR2DL2:GKA-Cw3). The interface of the complex was found to be dominated by charge complementarity, and mutations altering the existing salt bridges diminish binding substantially. Allotype specificity seems to be conferred by a specific hydrogen bond between Lys44 (KIR) and Asn80 (Cw3).

The structure of mitochondrial transcription factor mtFB, presented by F. Schubot, was solved by Xe-derivatization with data collected in a conventional X-ray source. Unexpectedly, the structure revealed a fold clearly related to the ErmC' family of rRNA-methyltransferases. The full implications of this finding are still being explored. F. van den Akker presented the structure of the glycosylated, dimerized hormone-binding domain of the atrial natriuretic peptide (ANP), a member of the G-coupled hormone receptors. The structure reveals two modes of allosteric control. One is related to the similarity of the fold to type I periplasmic binding proteins, suggesting a conformational change induced by small molecular effectors. Of particular interest was the proposed second switch related to the presence of a conserved chloride-ion binding site and its role as an allosteric effector. S. Greasly presented the structure of avian ATIC (also known as PurH), a bifunctional enzyme possessing transformylase (AICAR Tfase) and inosine monophosphate cyclohydrolase (IMPCH) activities at 1.75 Å resolution. Its role in the penultimate and final steps in purine biosynthesis makes ATIC a prime target for rational drug design. The IMPCH domain is at the N-terminus, while the AICAR Tfase activity is at the C-terminus. It exhibits a novel fold and the identified active sites are 50 Å apart, with no obvious tunnel connecting the active sites. J. Harp presented the 2.5 Å structure of the nucleosome core particle using data derived from one crystal grown in microgravity. This resolution allowed the analysis of the subtle asymmetries found in an otherwise symmetrical particle. Of particular interest was the location of the dyad of the histone octamer, which was found to pass through base 73, rather than in-between base pairs 73-74, as expected. Two five-minute presentations were added at the end of the session. J. Zhang described the main features of flavoprotein ubiquinone oxidoreductase complexed with ubiquinone, where the ubiquinone molecule partially penetrated into the membrane-bound part of the enzyme. Finally, R. Stenkamp discussed the main features of the recently solved structure of bovine rhodopsin at 2.8 Å. The similarities and differences with the better-characterized bacteriorhodopsin raised considerable interest. If they have not already appeared, we are eager to read the details of all the interesting structures reported at the session in forthcoming papers.

Cele Abad-Zapatero

Structure-Based Drug Design, 02.03

The Structure-Based Drug Design Session combined speakers from academia, government research labs and the pharmaceutical industry. The session was very well attended and demonstrated that Structure-Based Drug Design is an exciting area for research that is now recognized as an essential component for any successful, state-of-the-art portfolio in Drug Discovery. A number of the speakers demonstrated the power of combining combinatorial chemistry with structure-based approaches and the last speaker made the case that crystallography, like NMR, can be used in screening.

Pat Weber from Schering Plough Research Institute opened the session by presenting an overview of the impact and role of structural biology in the drug discovery process emphasizing three areas: structure-based drug design, target selection, and structural genomics. Structure-based drug design is a widely accepted core technology in the pharmaceutical industry because of its ability to determine the precise interactions of the inhibitor with the target. In the Ras farnesyl transferase program, the SAR for a tricyclic inhibitor series included an essential carbonyl and a permissive stereo center. Structural studies of inhibitor-target complexes revealed the structural basis of the observations. In their nitric oxide synthase program, affinity for inducible NOS and selectivity against endothelial NOS were essential goals. Comparing structures of both human enzymes revealed identical active sites and that inhibitors targeting this region alone could not attain the required selectivity. Structural studies of HepC protease, helicase, protease-helicase, and polymerase combined with enzymology and modeling revealed not only the roles these proteins play individually, but their potential roles in a concerted activation mechanism.

Xinhua Ji from the National Cancer Institute described his work on glutathione-S-transferase. Because of its role in degradation of cancer drugs, inhibition of glutathione-S-transferase by generating nitric oxide in the active site, could increase the effectiveness of anti-cancer therapies. Of the three isoforms, α, μ and π, $\pi$is the predominant form in cancer cells. Comparison of the active sites and transition state analogs revealed a potential strategy for achieving selectivity vs. α and μ. The α-site is narrow so larger inhibitors do not bind to alpha. The π-site and μ-site have fundamentally different character and by changing the chemical characteristics of the inhibitor, preferential binding to the π-site was achieved. Application of this strategy has resulted in p-selective inhibitors and shown the power of using structural information on the transition state in rational drug design.

Virginia Rath from Pfizer described her work which has identified a novel phosphorylase allosteric binding site that can be exploited in drug design. Type II (non-insulin dependent) diabetes is a major health problem in the United States affecting 15.6 million people. Liver glycogen phosphorylase, an enzyme which degrades glycogen to glucose, is an allosteric enzyme and modulation of its activity represents a potential strategy for controlling blood glucose levels. By screening active enzyme in the presence of glucose, Pfizer identified compounds which reduced enzyme activity. Structural studies revealed two molecules bound in close proximity (6 angstroms) at a novel allosteric site at the dimer interface. Analogues based on the structure, including a dimer-like molecule that linked two chloro-indole rings have increased the potency and effectiveness of this series.

Jim Hogle from Harvard showed that combinatorial chemistry coupled with high resolution structural information allows efficient exploration of binding site space and character. Using the program MCSS, which decorates the binding site with thousands of fragments, a trial library of 75 compounds was identified for synthesis and analysis. A unique assay has been developed to identify tight-binding members of a library. Virus is exposed to the library, then purified and denatured. Bound molecules are then analyzed by mass spectrometry. Jim also presented a strategy for intervention in *herpes simplex* virus by disrupting the interaction between the polymerase and its processivity factor UL42. This interaction is dominated by the C-terminal helix of the polymerase. A combinatorial template based on a cyclohexane core has been designed that can present amino acid like side chains in a way that mimics one surface of a helix.

Dave Matthews from Agouron kicked off the second half of the session by describing a strategy for curing the common cold. Rhinovirus 3C protease presents several interesting challenges as a target for intervention, but foremost are the need to design drugs capable of binding to a shallow binding site and targeting multiple serotypes. In this program, neither high-throughput screening, nor *de novo* design yielded inhibitors suitable for further optimization. The strategy that was adopted was to design selective reactive compounds by fine-tuning the chemistry and character of the molecule to the binding site. Knowledge of the structure of covalent complexes helped guide this program to a molecule that is potent against 3C and has broad activity against multiple serotypes, but has no activity vs. a panel of cysteine and serine proteases.

Jim Sacchettini from Texas A&M described his work on transthyretin. Insoluble protein fibrils of the thyroxin carrier transthyretin (TTR) have been linked to several amyloid diseases. Inhibition of fibril formation has been linked to several non-steroidal anti-inflammatory drugs which bind TTR and stabilize its native conformation. The two-fold symmetric binding site of TTR presented a challenge to structure-based drug design because of a need to interpret the density for molecules in multiple conformations. This became a strength as numerous structures were solved. As the character of the binding site was revealed, it became possible to design two-fold symmetry into

the compounds resulting in tighter binding molecules.

Vicki Nienaber from Abbott closed the session by describing a new screening role for crystallography in the pharmaceutical industry. Crystallography is most often looked at as a tool for understanding inhibitor binding, not for discovering novel molecules. Now, however, Abbott has developed a method in which crystals of the target are soaked in mixtures (presently 100 compounds, but up to 200) and binders are identified by electron density difference maps. The method has been used successfully in several programs and is undergoing robotic automation including technology capable of mounting and aligning crystals. This will allow for very high-throughput data collection and screening (up to 10,000 compounds in two weeks).

Bruce Jacobson and Bill Stallings

Protein-Nucleic Acid Interactions, 02.04

Session chair: Cynthia Wolberger

The structures presented in this session shed light on a wide range of biological processes that depend upon interactions between proteins and nucleic acids. Topics ranged from novel DNA-binding domains to enzymes involved in DNA replication, repair, and regulation of DNA topology to proteins involved in interactions with RNA. The first speaker, Tom Ellenberger (Harvard Medical School), presented structural studies of the replicative DNA helicase from phage T7. The helicase domain crystallizes in a 6_1 helical array reminiscent of that formed by the *E. coli* RecA protein, with nucleotide binding occurring at the subunit interfaces. A second crystal form showed a different organization, with helicase subunits forming a flat, hexameric ring reminiscent of that seen in electron micrographs, but with variations that deviate from perfect 6-fold symmetry. These different arrangements may reflect the different conformational states adopted by the hexamer during its reaction cycle.

This elegant presentation was followed by that of Robert Batey (Yale University), who described RNA-protein interactions in the signal recognition particle (SRP). The SRP54/Ffh protein binds to the highly conserved domain IV RNA, using side chains conserved among different species. The structure contains a number of surprising features, including novel base pairs in the RNA and the presence of a helix-turn-helix motif that is not, however, used in nucleic acid binding. Bart Staker (University of Michigan) continued the discussion of RNA-protein interactions in his presentation of the structure of the heat shock protein, Hsp15. This protein, which is thought to be involved in ribosome repair, adopts a previously unrecognized RNA-binding fold. Since sequence comparisons show that this motif occurs among a wide range of proteins that bind RNA, the structure of Hsp15 paves the way to an understanding the various members of this new RNA-binding motif family.

Following the break, we heard Wei Yang (NIH) talk about her structural studies of bacterial proteins involved in DNA mismatch repair. MutS, which has ATPase activity, recognizes the mismatch while MutH is an endonuclease that cleaves up to 1kb from the recognition site. The endonuclease is activated in the presence of ATP by the complex formed by MutS with mismatched DNA and with MutL, a mediator between MutH and MutS. The Yang group has been dissecting how these proteins cooperate in mismatch repair through structural studies of MutH, MutL and, now, MutS. The crystal structure of MutS bound to a DNA mismatch shows how the DNA kinks and the mismatched base flips out from the double helix and forms interactions with the protein. The stacking of a Phe on the unpaired base explains how the protein stabilizes this base conformation. Since mismatches have generally been found to be stacked in the double helix, Dr. Yang presented a model whereby the protein scans the DNA looking for deformable mismatch-containing regions.

Patrick van Roey (Wadsworth Center) described a very unusual DNA-binding domain from the endonuclease, TevI. The structure of the 95 ordered residues bound to a 20 base pair DNA recognition site reveals that it contains not one, but three distinct DNA-binding motifs: a helix-turn-helix (HTH), a helix-strand linker, and a Zn finger domain. The HTH and Zn finger are smaller than the classical members of these respective families, further shrinking the definition of what constitutes a DNA-binding domain. These three domains snake along the DNA, forming mostly phosphate contacts, with the few base-specific contacts mediated by the helix-strand linker region.

Alfonso Mondragon (Northwestern University) concluded the session with insights into the mechanism by which type IA topoisomerases alter DNA topology. These enzymes relax negative supercoils and require the presence of a single-stranded DNA region for activity. Following up on his original structure of *E. coli* Topo I, Dr. Mondragon showed how a subsequent structure of a different fragment revealed a large conformational flexibility in the relative position of some of the protein domains that would allow the enzyme to encircle double-stranded DNA. Questions had remained, however, as to which active site residues participated in binding and cleavage of single-stranded DNA. In an exciting new development, the structure of Topo III (another typ1 IA enzyme) has been determined with bound single-stranded DNA. The structure not only reveals the binding site of the DNA, but shows that the presence of the DNA end in the active site causes a structural rearrangement as compared with the residue positions seen in the apoprotein. This new picture of yet another phase of the reaction brings us one step closer to understanding the complete topoisomerase mechanism.

Cynthia Wolberger

Problem Structure Determination, 02.06

This session left no problem unsolved even though it required in all instances an almost superhuman degree of persistence, determination and intelligence. The problems were of several

kinds, ranging from unruly behavior of proteins, entirely surprising crystal packing modes compounded by pseudo-symmetry, only just-enough selenium atoms for MAD phasing, to hair-raising twinning nightmares.

Stephen Price opened the session by telling the problems he had to solve in Kiyoshi Nagai's group working on a spliceosome-component, the U2A'-U2B" Protein RNA-Ternary Complex. Hammerhead ribozymes were employed, at both 3' and 5' ends, to obtain large amounts of the desired RNA *in vitro*. Various variants of the desired RNA were tried but a proper procedure to obtain monomeric RNA could not be found. This was finally overcome by denaturing the RNA in 6 M urea and mixing it, in a 1:20 ratio, with the U2A'-U2B" protein. This resulted in the proper RNA-protein complex for which crystallization conditions were then found in which 0.5% PEG 600 (not more, not less) was crucial. Crystals of the seleno-met protein failed to grow, hence heavy atom derivatives were aimed at, but heavy atom compounds shattered the crystals or changed the space group. By making various X to Cys and Cys to X substitutions, well-behaving crystals were finally obtained, phases were arrived at and the structure of this marvelous protein RNA complex was fully unraveled.

Next, Gabby Rudenko from the Deisenhofer lab described the structure determination of the LNS domain from neurexin 1β. Crystals were thin (10 μm) and fragile, and indicated in the self-Patterson, already a foreboding of troubles ahead by showing a very significant non-origin peak at (0.5, 0.4, 0.5). The number of seleno-mets per 226 residues was 2, so the crystals contain one per 113 residues with probably 4 subunits in the asymmetric unit. The selenium sites could be found relatively quickly and an interplay of crystallographic two-folds and non-crystallographic two-fold screw axes was arrived at to make sense of the self-Patterson. Finding the NCS operators for density averaging was next to impossible, but using non-top ranked peaks in a most noisy Pd difference Fourier, the NCS operators could be found. Four-fold density averaging indeed did the job and revealed the structure - which was entirely different than hitherto expected. There were not 4 but 8 subunits per asymmetric unit, each with only 178 amino acids out of 226 ordered. What was initially thought to be one subunit with 2 Se-mets turned out to be two subunits, each with only one Se atom persubunit ordered, related by a 134° rotation. Thus, only one Se per 178 amino acids was available for phasing. The calculated anomalous scattering differences were a mere 2.5%. The eventual structure was, of course, extraordinarily beautiful.

Celia Chen, from the Herzberg lab, described the structure determination of 2-amino ethylphosphonate transaminase, a protein with 11 Se-mets per 367 amino acid subunit and with somewhere between 44 and 88 selenium sites per asymmetric unit. Eventually, Sheldrick's Half-Baked procedure was able to find 66 sites, implying three dimers per asymmetric unit. In retrospect, Shake'n Bake also worked but discriminated less clearly between the top 66 and the next sites on the list. The self rotation function had given no sign whatsoever for any three-fold, but, instead, clear signals of two-folds. This puzzle was resolved by the packing of the dimers of which two were related by a two-fold while the third molecular two-fold was perpendicular to the other molecular two-folds. Next, WARP was used to trace the solvent-flattened map and when the various fragments of the partially traced subunits were superimposed a remarkably complete chain of the subunit was obtained. The moral of this and the previous talk was to keep eyes and brains wide open for unexpected, insidious, variants of the more trivial forms of non-crystallographic symmetry.

Next, Olga Mayans from the Willmans group in Hamburg described the problems with the structure determination of TrpD, a key enzyme in the tryptophan biosynthesis pathway. The self Patterson showed two peaks. The height of one of these varied per crystal. The space group was either P2 or $P2_1$ with a pseudo C2 diffraction pattern. Automated Patterson solving programs did not help, but manual procedures, with the real space evaluation program GETAX providing the non-crystallographic two-folds, helped in making progress. Some weak sequence homology to a dimeric protein with known structure led to imposing a local two-fold onto the structure and generating dimers. Olga was able to solve the structure in $P2_1$, although the space group was P2, because of the crystal packing. Eventually it turned out that not all subunits were equivalent - some being more open than others, and one subunit was quite disordered. Once this was all taken into account a well interpretable density was obtained and the saga yielded a well refined structure.

Hong Zhang talked about her struggles with the structure determination of geranyl geranyl transferase in the Deisenhofer lab. The 105 kDa heterodimer grew crystals which diffracted to 2.7 Å resolution and had space group P1. They were also clearly twinned. Strategies tried to overcome the twinning problem were: (1) Ignore - did not work; (2) Purify the protein more - no effect; (3) Use a new version of DENZO to process the two overlapping data sets separately and discard overlapping reflections - yielded a 70% complete data set but did not look robust enough to arrive at reliable isomorphous differences; (4) Use molecular replacement and a farnesyl transferase polyalanine model based on Cα coordinates from a stereo figure. This resulted in an electron density map but could not be pushed further towards a structure for the parts not in the model; (5) Finally, very carefully micro and macroseeding procedures resulted in a protocol which yielded large and, in ~30% of the cases, truly untwinned crystals - at least for part of the crystal volume. Some crystals showed no signs of twinning at the thin tip of the crystal, but considerable twinning at the thicker center. [In the discussion this phenomenon of uneven quality (twinning, mosaicity) across one single crystal appeared to have been observed in numerous other projects as well.] Xenon-phasing worked like a dream and an absolutely marvelous structure was obtained eventually.

The speakers in the session had each gone all-out to prepare slides illustrating the insidious nature of the problems encountered and the ingenious nature of the solutions to overcome them.

Wim Hol

Fibers 2K: Twists and Turns for the New Millennium, 03.01

Chairs: Dan Kirschner and Barry Farmer

The Fiber SIG organized a full-day session at the Annual ACA Meeting in St. Paul, featuring eleven speakers representing the diversity of research from biological to materials science in this area. Numerous biological molecules and substances of industrial interest do not form crystals, and so when analyzed using diffraction techniques they are studied as fibers that have varying degrees of orientation and disorder. Some of the challenges that face investigators of such materials include preparing homogeneous samples having a high degree of orientation and/or order, collecting data from very weakly scattering samples, interpreting the diffraction patterns which may have a paucity of reflections or have sharp Bragg reflections superimposed on diffuse intensity maxima, and developing molecular models at atomic resolution that account for the diffraction patterns and are also physically plausible.

Terry Kraft (Medical School, Hannover, Germany) described how her synchrotron X-ray studies of single muscle fibers were able to distinguish between different structural states of the cross-bridges. Tom Irving (Illinois Institute of Technology) presented results from small, weakly diffracting specimens, including flight muscles from water bug and *Drosophila*, and thereby demonstrated the usefulness of the undulator BioCAT beamline at the Advanced Photon Source (Argonne, IL). Rick Millane (Purdue) gave a comprehensive description of the disorder problem in fiber diffraction, and how analysis of the disorder can be included in the structure determination. Christian Riekel (ESRF, Grenoble) presented his microdiffraction results from synchrotron X-ray studies of single fibers of spider dragline silk, and demonstrated how the structural features of the silk depend on the spinning speed and distance from the silk gland spigot. Ted Atkins (Bristol, UK) described correlated X-ray fiber diffraction and transmission electron microscopy analyses that were focused on elucidating the structures and folding mechanisms of nylon-6 oligomer crystallites containing different numbers of amide units. Mark Shotton (Daresbury Lab, UK) updated the latest in CCP13 software development for analysis of fibre [sic] diffraction patterns. David Kaplan (Tufts University) demonstrated how the incorporation of methionines or enzymatic phosphorylation sites into recombinant spider dragline silk proteins can be used to trigger and control the macromolecular assembly of polyalanine rich sequences into fibers for *in vitro* models of fibrillogenesis. Jennifer Taylor (Stevens Institute of Technology, Hoboken NJ) described how high spatial-resolution electron diffraction was applied to analyzing orientational order parameters and skin-core structures in drawn versus annealed fibers assembled from rigid liquid crystal polymers. John Blackwell (CWRU, Cleveland OH) presented arguments for deducing the three phase amorphous-orthorhombic-hexagonal structure in isotropic and drawn samples of poly(ethylene-co-octene) from small- and wide-angle X-ray diffraction data. Kenn Gardner (Dupont, Wilmington DE) detailed his analysis of X-ray and electron fiber diffraction from a synthetic silk, suggesting a fourth packing mode for this glycine-alanine rich polymer. Stephen Cheng (University of Akron) reviewed protein secondary and tertiary structure as a prelude to describing the different levels of chirality in macromolecular assembly in general, and in particular in his unusual helical lamellar crystals that assemble from a liquid crystalline polymer, and whose structure was analyzed by correlated electron diffraction and wide-angle X-ray diffraction. The FiberSIG presentations briefly summarized above demonstrated not only the common methodological and analytical interests among fiber diffraction practitioners, but also the common structural themes among biological, non-biological, and biomimetic substances.

Dan Kirschner and Barry Farmer

General Interest Group Sessions, 04.01

The General Interest Group (GIG) of the ACA differs from the Special Interest Groups (SIGs) in several important ways. It provides a forum for authors who find that the SIG sessions are either too narrowly focused or do not cover the topics in which they are interested. GIG sessions have no invited speakers and are not organized around preselected themes. The papers at St. Paul were all drawn from submitted abstracts and consequently the themes of the three sessions reflected the current interests of the members of the ACA. As a result, the GIG sessions had a more catholic flavour than most of the SIG sessions. The papers covered crystallography from materials science to biology and from instrumentation to theory, giving the large audience an overview of the current state of crystallography.

Particularly impressive was the description of a compact sealed-tube X-ray generator given by Graham Fraser. Using only 24 watts, this generator uses state-of-the-art electron and X-ray optics to produce an X-ray beam that is competitive with

that from a rotating anode generator. The use of a CCD detector with a diamond-anvil high-pressure cell was the topic discussed by Michael Ruff. He showed how the software can identify and subtract the diffraction pattern of the diamond single crystals while providing the same coverage as a conventional diffractometer.

After the measurement of structure factors comes the determination of phases. A technique currently attracting interest is single-wavelength anomalous scattering or diffraction (SAS or SAD, the potential confusion between the acronyms for Single-wavelength Anomalous Scattering and Small Angle Scattering was pointed out during the discussion). Unlike MAD, SAD only needs measurements at one wavelength. It requires the presence of a heavy atom which often has to be added to the native protein, but an alternative is to use sulfur which is present in all proteins. The anomalous scattering of sulfur is weak and its absorption edge is too low for most synchrotrons, but Gary Newton showed an impressive electron density map calculated with phases obtained from a standard laboratory copper source. A different approach was described by Jeffrey Roach who used the Sayre equations to refine and extend phases from the sums and differences of the amplitudes of Bijvoet pairs measured in a SAD experiment.

For most structures refinement is straightforward once the phases are approximately known, but Judith Flippen-Anderson's analysis of the Cambridge Structural Database suggests that the number of disordered structures is growing, either because we are now better able to recognize disorder when it is present or because we feel more confident about refining such structures. Two talks demonstrated that disorder is easier to analyze if the diffraction pattern is measured to high resolution. In a study of small organic molecules, Jeffrey Deschamps noted that it is precisely in the disordered regions of a crystal that one gains by using high resolution measurements. As if to confirm this observation Boguslaw Stec, standing in for George Phillips, convinced us that the reason why the Fe-C-O bond in carboxymyoglobin was originally reported as bent was that the measurement was made on a disordered crystal at low resolution. Lief Hanson pointed out that the way to make measurements at high resolution was to keep the sample at helium temperatures since this significantly reduces the noise at high diffraction angle.

Abe Clearfield gave his past-president's speech at the Annual Banquet

Dr. Purnell Choppin, President Emeritus of the Howard Hughes Medical Institute, received the ACA's Public Service Award and gave the keynote speech at the Annual Awards Banquet

Symmetry is another topic of continuing interest to crystallographers. Bob Sparks did not actually recommend that we refine all our structures in P1 and use his program FINDSYM to select the space group, but it looked like an attractive approach for a structure solver with few crystallographic smarts. The danger of such an approach is that it can mask a number of problems such as twinning, which was the topic of a talk by Regine Herbst-Irmer who showed us the best way of dealing with non-merohedral twinning using programs such as GEMINI and SHELXL. Carroll Johnson introduced us to an algebraic method of describing both space group symmetry and pseudosymmetry and suggested that we may be hearing more about groupoids in the future.

Following the determination of a structure comes its interpretation. Concerned that many of us hold contradictory beliefs about the nature of bonds, David Brown presented a coherent picture of the chemical bond in inorganic compounds. Other speakers were interested in molecular packing and their talks showed the range of problems that packing involves. Carol Brock noted that some organic compounds have up to nine different molecules in the asymmetric unit, a phenomenon which she attributes to modulations of the structure resulting

from the competition between two modes of packing. Jeffrey Bell described an ambitious theoretical and experimental project to improve the crystallization of proteins by providing them with surface residues that have a high probability of forming strong links to neighboring molecules. Packing was also a concern for Gary Enright who introduced us to the packing of tert-butylcalix[4]arene inclusion compounds. Marilyn Olmstead suggested that co-crystallisation was the way to grow crystals of fullerenes large enough for X-ray studies. This technique has the additional advantage of preventing the molecules from rotating and thus allowing accurate measurement of their geometry. In an elegant talk, Wally Cordes introduced us to an electrically conducting complex aromatic molecule with no close intermolecular contacts, leaving us to guess how the electrons managed to jump between the molecules.

A couple of talks described the use of the web in crystallographic education. Tom Proffen told us about a web version of the program DISCUS that provides simulations of diffuse scattering from defect structures. The web interface is simple enough that the students are able to concentrate on the science rather than the details of manipulating the files. Katherine Kantardjieff described the Keck Foundation Center for Molecular Structure which uses the web to link 23 campuses of the California State University. The web provides undergraduates with remote access to the Center's diffractometers as well as to interactive courses and tutorials. These talks gave us a glimpse of a world in which our science will be secured to future generations through virtual schools of crystallography, even as our traditional schools are closing down. Our science continues even though the methods change.

Not all the papers submitted under the heading of General Interest were included in the oral sessions. Fifteen of the more technical presentations covering the same broad range of interests were presented as posters, an arrangement that gave the participants an opportunity to interact more directly with the author.

I. David Brown

Mert and Wade Adams came to the meeting to visit with friends, including those made while they operated the Polycrystal Book Service.

New Science Using New Neutron Sources and Instruments, 05.01

It is the worst of times, it is the best of times — with respect to American science using neutron measurements. In the past year, of the five major neutron centers in the United States, one was formally closed, another did not operate and a third is preparing to shut down for an upgrade. On the other hand, during this same year, exciting neutron measurement capabilities have become available, due to the completion of new instruments. Furthermore, in the past year, ground was broken for the Spallation Neutron Source (SNS), a next-generation neutron facility that will be as important for the field's future as the 2nd and 3rd generation synchrotrons have been for X-ray work.

The Neutron SIG organized a session titled "New Science Using New Neutron Sources and Instruments" to highlight the exciting science now being done in the U.S. and to look toward the new science that will be possible with the SNS. The decision to focus on U.S. facilities was made reluctantly, as many of the most exciting developments in the field are taking place at centers outside the U.S. Limited funding restricted the speakers who could be invited.

The first three talks shared a biological theme. Chuck Majkrzak (NIST) introduced neutron reflectometry, showing how neutrons can be used to probe a single monolayer. He also explained how changing the neutron contrast from the fronting or backing layer is used to directly determine the phases of the scattered neutrons, allowing the determination of the 1-D scattering density without any *a priori* assumptions. As an example, he presented structural information for mellitin hybrid bilayer membranes determined from neutron reflectometry and molecular dynamics results. Kent Blasie (University of Pennsylvania) then summarized his group's studies of monolayers of cytochrome C using X-ray reflectometry, EXAFS and neutron reflectometry. Building on the X-ray results, the neutron studies were able to characterize the water distribution in this system. Jill Trewhella (Los Alamos) began her talk with a gripping description of the destruction wrought by the recent forest fire that devastated the Los Alamos area. She then summarized her work over recent years developing models for the structure of troponin C and troponin I complexes using neutron small angle scattering, as well as drawing on crystallographic, NMR and computational results.

After the coffee break, the session resumed with three talks

on crystallographic studies of oxide materials — where neutron measurements were essential. Patrick Woodward (Ohio State) presented temperature-dependent structural distortions, as well as magnetic and charge ordering phenomena, in the $(Sr,Nd)MnO_3$, $(Ca,Nd)MnO_3$ and $(Ca,Bi)MnO_3$ perovskites. For this work, synchrotron X-ray powder diffraction was crucial for phase and symmetry assignments, while neutron powder diffraction gave information on magnetic ordering and accurate M-O distances and M-O-M angles. Jason Hodges (Oak Ridge/Argonne) contributed a talk on structural studies in the $SrFeO_x$ perovskite system, motivated by their potential applications for ceramic gas-separation membranes. In these systems, multiple structural models, with fits of comparable quality to the diffraction data were found, but one model appeared correct based on a bond valence analysis for the cations. Bryan Chakoumakos (Oak Ridge) then presented a contributed talk on his studies of the amblygonite ($LiAlPO_4F$) to montebrasite ($LiAlPO_4OH$) solid solution system, based on neutron single crystal measurements. A careful temperature-dependence study demonstrated a disorder of Li atoms created by a structural variation associated with F substitution.

The afternoon session, chaired by Bryan Chakoumakos, had a materials physics focus. The first three talks highlighted inelastic neutron scattering. Dan Neumann (NIST) gave an overview of the technique. He then provided examples where neutron spectroscopies give unique insights into dynamics: clathrate vibrational modes studied with inelastic scattering; cubane group motions and α-lactalbumin folding dynamics, studied by quasielastic scattering; as well as glass, polymer and buckyball studies of proton dynamics with spin echo spectrometry. Taner Yildirim (NIST) followed up with an animated presentation (both literally and figuratively) demonstrating the value of combining first-principles quantum computations and inelastic neutron scattering. Examples of his work included additional information on cubane, hydrogen diffusion in protonic conductors, and modeling of negative thermal expansion. Collin Broholm (Johns Hopkins) presented magnetic structural studies of quantum magnets using inelastic scattering instrumentation around the world. His study focused on the "instantaneous magnetism" induced by impurities in Y_2BaNiO_5.

The final two talks used radial distribution function (RDF or PDF) techniques to study disordered or liquid systems. Simon Billinge (Michigan State Univ.) showed how the PDF technique is used to study the details of local structure in what he calls "crystallographically challenged" (a.k.a. disordered) materials. One excellent example he gave was polarons in manganites, where local Jahn-Teller distortions are not reflected in the long-range crystallographic structure. John Turner (Univ. of Tennessee) presented results where selective isotopic substitution was used to study structure and coordination of organometallic moieties in solution.

The session ended with a moderated discussion on new instrumentation planned for the SNS. Jason Hodges presented an impromptu overview of the currently planned suite of instruments and their contact scientists. Simon Billinge then prompted a vigorous and amicable debate on the need for a medium-length flight path diffraction instrument for PDF work on crystallographically challenged materials. Using data from the GEM instrument at ISIS, he demonstrated how the planned complement of diffraction instruments would not meet the challenges of local-structure studies in crystals. It is hoped that this will provide the starting point for the planning of a new diffraction instrument.

Brian Toby

Service Crystallography at Synchrotrons, 07.01

The half-day session "Service Crystallography at Synchrotrons" (07.01) was organized to survey the status, the scope, and the future of widespread user access to beamline diffraction experiments.

Bob Sweet of Brookhaven National Lab's Biology Department opened the eyes of the large morning-after-the-mixer crowd by bringing the future to St. Paul. He demonstrated a suite of software tools which allow a remote user to have control over the experiment, watch the diffraction images on the fly, monitor the beam conditions, and have live video and voice communication with the technician at the beamline. Since the researcher needs only to use a Java-capable Web browser to connect to the experiment, any networked computer in the world can act as the console. The package, although optimized on a National Synchrotron Light Source (NSLS) protein line, has modules which can (and will) be modified and distributed to assist in service work for a variety of beamline operations.

Elizabeth MacLean, of the Daresbury Analytical Research & Technology Service (DARTS) presented an excellent model for running an efficient, multifaceted fee-for-service facility for a range of industrial clients. The key to the operation at Daresbury Laboratory's Synchrotron Radiation Source (SRS) is a core staff of experimentalists providing expertise in areas such as small molecule single crystal analyses and powder diffraction. The diversity of techniques available around the ring, from infrared microscopy to protein crystallography, can be offered to DARTS clients by distributing projects to designated industry contacts on the appropriate beamlines. The analytical or characterization technique or set of techniques required to quickly solve a client's problem can be determined and assigned centrally. Everyone benefits.

Bill Clegg of the University of Newcastle upon Tyne's Chemistry department described some remarkable studies on

microcrystals and poorly diffracting single crystals undertaken at the chemical crystallography station at the Daresbury SRS and other synchrotron facilities. He emphasized the importance of having a dedicated line to allow the throughput required to offer an effective service. Bill outlined a proposal on the books in Britain for a central crystallography service for academics, which would collect either lab source data or synchrotron data, as dictated by the sample. This would allow the experts to efficiently schedule samples at the most heavily used station on the ring.

After tea, big brother Dick Harlow introduced us to some of the gruesome realities of surviving at an Advanced Photon Source (APS) beamline where one can spend up to 25% of one's beamtime catering to rookies. His solution to the problem was a proposal to train a dozen or so of the ACA's Service or Small Molecule SIG members to safely operate the DND-CAT's small molecule equipment as "semi-service" operators. They, in turn, would each gather samples from a number of different labs and collect a series of data sets over a period of two or three days. A group proposal would be peer reviewed, and the researchers would compensate the traveler in a suitable manner. This would make efficient use of both beamtime and staff time. The idea was welcomed with open arms by the SIG members . . . almost too many arms! There will have to be a vote to see who gets to go.

The final presentation was a tag-team event, in honor of our host state, delivered by Jim Viccaro (Univ. of Chicago) and David Cookson (Australian Nuclear Science and Technology Organization) from APS. They outlined a variety of insertion device and bending magnet stations at ChemMatCARS and GeoCARS, either in operation or being commissioned. The available experiments include state of the art SAXS/WAXS, high resolution powder diffraction, microcrystal and tunable anomalous dispersion single crystal diffraction, surface and interface (including liquid-liquid!) scattering, and more. Polymers, solid-state materials, molecular compounds, geological crystals, thin films etc. will be studied. These beamlines are operated as a U.S. National Facility, and have a mandate to provide 75% of their photons to users. A good portion of this will have to be achieved in service mode.

Lee Daniels and Maren Pink receive the ORTEP-of-the-Year award from Dick Harlow at the Service Crystallography and Small Molecule SIG dinner. Note: the award is won for bringing attention to interesting ORTEP figures.

The session as a whole gave the listeners the sense that in the near future chemists, biochemists, geologists, materials scientists, and physicists will have easy and inexpensive access to some very powerful diffraction experiments. The management models and choices of experiment design and control used to operate these facilities in a manner which encourages their widespread use were especially appreciated by those involved in setting up future synchrotron service labs, such as ChemMatCARS or the Canadian Light Source. The role of the service crystallographer in linking academic and industrial researchers to this powerful array of analytical techniques is a critical component in the success of these beamlines.

Jim Britten

Advances in Small-angle Scattering Instrumentation and Data Analysis, 08.01

The morning session of the Small-angle Scattering Special Interest Group was titled, "Advances in Small-angle Scattering Instrumentation and Data Analysis". The session was chaired by Harry Brumberger.

Paul Butler (ORNL) led off the meeting with a discussion of near-surface SANS (NS-SANS), a new small-angle scattering technique that characterizes microstructure in a reflection geometry, i.e., with the plane of the sample nearly parallel, rather than perpendicular, to the incident beam. Paul illustrated this technique with a study of several surfactant systems under shear that showed the differences between near-surface and bulk structures.

Pete Jemian (U. of Illinois) described the opportunities and challenges in using anomalous small-angle scattering (ASAXS) to generate quantitative information in systems containing multiple inhomogeneities of similar size. He illustrated the method with two case studies conducted at the UNICAT sector of the Advanced Photon Source. Pete showed the importance of utilizing a continuously tunable X-ray energy to approach an absorption edge (associated with one of the inhomogeneity populations) from below.

Otto Glatter (U. of Graz, Austria) and Dmitri Svergun (EMBL, Hamburg, Germany) updated the audience on their

data analysis methods and software packages: Otto's group has successfully developed algorithms for determining both the structure factor S(q), and form factor P(q), in dense (interacting) particulate systems using a model-independent form factor. Dmitri demonstrated the ability of his algorithms to determine both shape and internal structure of macromolecules using SAXS and contrast variation SANS. Unlike protein crystallography, small-angle scattering yields protein structure information in liquid environments.

John Barker (NIST) described the new NIST/NSF funded USANS Bonse-Hart instrument (2×10^{-5} Å^{-1} < q < 0.01 Å^{-1}) at the NIST Center for Neutron Research. John explained how recent major advances in understanding the effects of the crystal thickness in USANS experiments have been combined with an innovative pre-monochromator design to produce a truly world-class USANS instrument.

Gerard Bunick (ORNL) updated the audience on the new cold source developments at HFIR including the new SANS instrumentation. Principally, this will consist of two new SANS instruments: a medium-resolution 35 m SANS mainly for biology, and a high-resolution 40 m SANS. The performance of these instruments will be comparable with the world's best SANS instruments, and they should be operational in 2002.

Thomas Rieker and Andrew Allen

Materials Structure at Long Length Scales: Recent Discoveries, 08.02

The afternoon session of the Small-angle Scattering Special Interest Group, "Materials Structure at Long Length Scales: Recent Discoveries" generated a great deal of discussion among its attendees. The session was chaired by Tom Rieker.

John Barnes (NIST) began with a demonstration of the importance of collecting 2-D SAXS images using orthogonal sample orientations when studying the 3-D lamellar structure of semi-crystalline polymers. David Londono (DuPont) the only industrial speaker in the SAS sessions, discussed crazing (void introduction) in rubbery polymers. Sanat Kumar (Penn State) rounded out the discussion on polymers with an energetic talk on the structure of ultra-thin polymer films. Sanat's talk generated a lively discussion of model dependent SANS data interpretation.

There were two talks on self-assembling systems, presented by Steven Kline (NIST) and Bruno Deme (ILL). Steve demonstrated the ability to lock in structure in a network of rod-like micelles using a polymerizable counter-ion. This system may prove useful for the preferential uptake of oil or other small molecules. Bruno Deme discussed crystallization of surfactant molecules to form micron diameter disk shaped particles a few tens of Ångstroms in thickness. His contrast variation experiments show that the surfactant molecules organize with hexagonal packing within the disc shaped particles.

Pappannan Thiyagarajan (ANL) provided a structural biology talk. He showed that RNA which is in an extended form in an aqueous environment folds with the addition of Mg ions. With high loading of magnesium, the RNA takes on a corpuscular shape.

Andrew Allen (NIST), the 2001 SAS SIG Chair, finished the session with a discussion of micro-cracking in textured ceramics. He demonstrated the advantages of the new USAXS instrument incorporating transverse reflections orthogonal to the main USAXS optics. This instrument, although of the Bonse-Hart type, provides pinhole-like data, not slit-smeared data. Thus it is the instrument of choice to study anisotropic materials at long length scales.

Tom Rieker

Crystal Engineering, 09.02

The day-long session Wednesday was conceived as an opportunity to explore the evolution of Peggy Etter's ideas about hydrogen bonding, cocrystals (or, molecular solid-state compounds), solid-state reactions, and the complementarity of crystallography and solid-state NMR. Thanks to Doyle Britton's efforts, a number of Peggy's students and co-workers, many of whom are not ACA "regulars", either spoke in or attended the session, which drew a good crowd. The focus was very much on the present and future; one of the now-retired ACA presidents said he was impressed by how much progress had been made during the last few years.

Jim Loehlin started out by describing saturated H-bonded cocrystals (e.g., R-NH_2^+R'-OH) and then went on to describe his efforts to grow layered cocrystals (e.g., R-NH_2/R'-OH/R-NH_2/R"-OH/R-NH_2/...) by aiming four molecular beams at a central rotating crystal seed. Although the diffraction patterns for the crystals obtained so far are extremely weak, the photographs of some of the crystals were impressive. Kraig Wheeler, and later Ray Davis, talked about their research on quasiracemates, which are cocrystals of two very closely related molecules (e.g., CH_3 and Br derivatives) that would be

enantiomers if they had the same composition. The cocrystals form because even approximate inversion centers are so advantageous for crystal packing.

Zofia Urbanczyk-Lipkowska described a class of solid-state reactions: the reaction of 2,4-dinitrophenylhydrazine with aromatic aldehydes to form polar hydrazones. The reactions are 100% complete in 12-24 hrs but proceed even more rapidly in Nujol. Joe Lauher described an impressive set of experiments in which H-bonded cocrystals were designed so that di- and tri-acetylene components (e.g., HOOC-CH_2CH_2-CCCCCC-CH_2CH_2 COOH) would be aligned for polymerization. In one case the alignment was so favorable that it proved impossible to determine the precise structure of the unpolymerized cocrystal.

Henrik Goerbitz described a series of dipeptide crystals (mostly built from alanine and valine) that form porous solids that include water or methanol in channels. Since the channels are too small to include higher alcohols, the compounds could be used to remove MeOH from solvent mixtures. Susan Reutzel-Edens emphasized the complementarity of crystallography and solid-state NMR in the pharmaceutical industry, especially when polymorphs and pseudopolymorphs (or, solvates) must be identified. She mentioned one drug system for which 25 solid phases, some of which grow concomitantly, have been discovered. Because individual crystal forms are patentable, the phenomenon of polymorphism represents an opportunity, as well as a problem, for the pharmaceutical industry.

After lunch, Lee Brammer talked about H bonding of metal halide ligands, which he and collaborators have studied using the CSD and high-level QM calculations as well as crystallography. Doyle Britton reported work on the three isomers of $C_6Cl_4(CN)_2$ and on their compounds with C_6Me_6. Many structures, some of them polymorphs, some of them disordered, had been determined. A rule for hexagonal tiling (i.e., a structural motif) was deduced from those structures: each cyano group should be near two Cl groups from adjacent molecules.

It would have been impossible to have a session dedicated to Peggy Etter without including talks by several graduate students.

Ali Rashid showed that cocrystals of p-nitroaniline (p-NA) with beta-cyclodextrin and with deoxycholic acid display nonlinear optical properties although pure p-NA does not. Sarah Mandel described the solid-state photochemistry of a series of triplet alkyl nitrenes derived for alpha-azido acetophenones.

The session concluded with Gabriela Diaz de Delgado's talk on structure, properties (e.g., magnetic behavior), and reactivity of Group IA and IIA salts of unsaturated dicarboxylic acids. It had been a great day for looking both forwards and backwards, and there had been a great deal to see in both directions.

Carol Brock

Pauling Prizes

Awarded to outstanding posters presented by graduate students.

Poster P033
Low Resolution Sulfur "Super Atom" SAS Phasing of Macromolecules Containing Disulfide Bonds. Chun-Jung Chen, John P. Rose, Gerold Rosenbaum, Bi-Cheng Wang.

Poster P122
Temperature- and Humidity-Dependent Cation Relocation in Zeolites: Pb-RHO. Yongjae Lee, Glover A. Jones, Jonathan Hanson, Andrea Freitag, John B.Parise, John Z. Larese, David R. Corbin, Volker Kahlenberg.

Poster P188
Crystal Structures of Polygalacturonase from Aspergillus aculeatus at Two Different pH's. Cho Sang Woo, Shin Whanchul.

Poster P196
High Resolution Crystal Structure of Isocitrate Dehydrogenase from Bacillus subtilis. Satinder K. Singh, David C. LaPorte, Leonard J. Banaszak.

Poster P225
A Novel Microporous Niobium Titanate: Structure Solution of an Octahedral Molecular Sieve from a 5 x 8 x 8 Micrometer Twinned Crystal Using Synchrotron X-ray Sources. Akhilesh Tripathi, John Parise, Nyman May, Tina M. Nenoff.

Honorable Mentions

Poster P125
Crystal Structure of a Novel Red Copper Protein from Nitrosomonas europaea. Raquel L. Lieberman, David, M. Arciero, Alan, B. Hooper, Amy C. Rosenzweig.

Poster P156
Designing Self-Assembling Multimeric Protein Cages and Filaments. Jennifer E. Padilla, Christos Colovos, Todd O. Yeates.

Selection Committee: Bruce Jacobson, Chair, Qi Gao, Joshua Sakon, Tom Zarembinski, and Tim Rydel

Winners of the Pauling Prize Awards

Oxford Poster Prize 2000

Awarded to a poster making use of cryo-crystallographic techniques.

Poster P222
Cryocrystallographic Structure of Lipovitellin Reveals Bound Lipid Molecules within the Major Cavity. James R. Thompson and Leonard J. Banaszak.

Selection Committee: Albert Beghuis, chair, Lisa Edberg, Matt Benning, Cory Momany, Corey Strickland

Peggy Etter Student Travel Awards

Mathew Kimber, Poster P106, *β- Carbonic Anyhydrase Active Site Architecture is a Mirror Image of that of α- Carbonic Anhydrases.*

Joanna Clark, Poster P039, *Snapshots of Molecular Recognition in Cyclodextrin Complexes with Derivatized Amino Acids - Perturbing the System with Changes in Functionality and Kinetic Energy*.

Akhilesh Tripathi, Poster P225, *A Novel Microporous Niobium Titanate: Structure Solution of an Octahedral Molecular Sieve from a 5 x 8 x 8 μm Twinned Crystal Using a Synchrotron X-ray Source.*

Connie Chidester with Joanna Clark, Akhilesh Tripathy and Mathew Kimber, winners of the Peggy Etter Student Travel Awards

TRAVEL GRANT APPLICATION

Limited funds are available to help students and young scientists attend the **2001 Annual ACA Meeting** in Los Angeles, July 21-26. Preference will be given to those presenting a paper or poster. To apply for assistance, send this completed form, a **copy** of the abstract you plan to submit and a supporting letter from your research advisor. The first deadline for applications is **January 31, 2001**. Applications received after this deadline will be reviewed only if funds remain after the first review. The final deadline for applications will be March 2, 2001. Information about travel to and lodging in Los Angeles is available at www.hwi.buffalo.edu/ACA/ACA-Annual/LosAngeles/LosAngeles.html

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Iain Duncan Mackie
Univ. of Edinburgh

Sarah Mandel
Univ. of Cincinnati

Johanna Mazlo
Univ. of Nebraska-Lincoln

Matthew Miller
Northwestern Univ.

Eliud Oloo
Univ. of Saskatchewan

Xiang Ouyang
Texas A & M Univ.

Thomas Proffen
Michigan State University

Oksana Pryma
National Taras Shevchenko Univ.

Ali Rashid
Univ. of Nebraska

Jeffrey Roach
Univ. of N. Carolina at Chapel Hill

Vivian Saridakis
Univ. of Toronto

Florian Schubot
Univ. of Georgia

Carrie Stover
NIST

Wolfram Tempel
The Univ. of Georgia

Akhilesh Tripathi
State Univ. of NY

Elena Vinogradova
National Taras Shevchenko Univ.

Amy Wernimont
Northwestern Univ.

Jeffrey Wilson
Univ. of Arkansas

Ning Wu
Univ. of Toronto

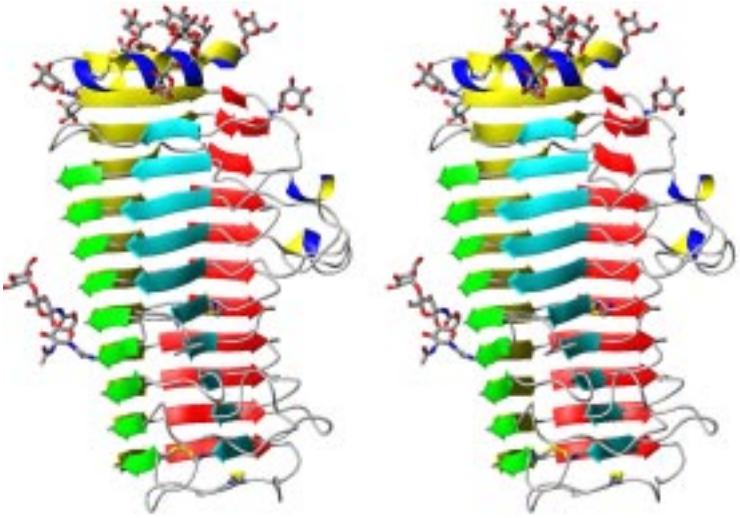
Hongliang Xu
Hauptman-Woodward Med Res. Inst.

Wei Zhang
Rice Univ.

Dear Travel Grant Fund Committee,

I would like to send my sincerest appreciation for providing the financial means which allowed me to attend ACA2000 in St. Paul. It was a great experience. I met many people. I also obtained specific advice for my project, which will accelerate the completion of it. This conference also allowed me to become more involved with ACA, especially YSIG. Thank you again for this enriching experience.

Johanna Mazlo
University of Nebraska



Overall schematic diagram of polygalacturonase from *Aspergillus aculeatus*. Obtained from the Pauling Award poster P188, *Crystal Structures of Polygalacturonase from Aspergillus aculeatus at Two Different pH's*. by Cho Sang Woo and Shin Whanchul.

It's Crystal Clear: Smarter Scientists Shun the Limelight

by Laura Billings, St. Paul Pioneer Press, July 27, 2000

Minneapolis pulled out all the stops this week for the 600 some animal geneticists who came to town for a much-publicized biennial conference. The city bought fancy new riot gear, set up concrete barricades, scared away Nicollet Mall shoppers, shut down Sommerfest, and arrested 81 animal rights protesters after dousing them with pepper spray.

Just the sort of red-carpet treatment that can give a scientist a pretty swelled head about her contributions to humanity.

Meantime, here in St. Paul, there were 700 scientists gathered at RiverCentre all week, talking about such sexy topics as genetic coding, erectile dysfunction, and something called "hot new structures." And do you think they got a single police escort, or one lousy front-page story in the paper?

Noooooooooo.

Granted, the work of the American Crystallographic Association scientists who study the structure of matter at atomic or near-atomic resolution isn't as attention-grabbing as those whose work involves cloning sheep, or dropping hazardous chemicals into the eyes of bunny rabbits.

Consequently, some crystallographers, whose work contributes to everything from atomic power to arthritis remedies, suffer from a certain inferiority complex. For instance, when I asked French scientist Vivian Stojanoff what she did for a living, she replied:

"I use X-rays from a synchrotron facility to locate the positions of atoms inside the molecule and when we know their positions and bond lengths we're able to make other substances to inhibit their activity. . . "

At this point, she threw up her hands in a flurry of apology. "It's just basic science. We don't get much attention."

True, no atoms are harmed in any of their experiments. "But you may hear the cries of yeast as they are grown and then slaughtered," said Doug Ohlendorf, a University of Minnesota professor, and conference program chair, who suggests the public and protesters may be a little late getting all worked up about animal genetics.

"It's been around forever. Minnesota's Haralson apple is the result of genetic manipulation," he said in a tone that indicated this science is just kid stuff.

"You know, probably more Nobel Prizes have been awarded to crystallographers than any other scientists," Ohlendorf said, noting that James Watson and Francis Crick, the big brains behind the double helix structure of DNA, were ACA types. "We're coming up with new discoveries all the time but we're just sitting over here, ignored."

Not that this obscurity weighed too heavily on Ohlendorf as we strolled through a display of papers to be presented (among them "Arginine: Structurally Underappreciated" and "Human Toposomerase I: Mechanistic Insights from Novel Covalent Complexes") and checked out a government Web site that logs the nearly 13,000 molecular structures charted so far. "The molecules are really neat to look at. They make good wallpaper," Ohlendorf said. (If you doubt this, check out www. rcsb.org/ and see for yourself.)

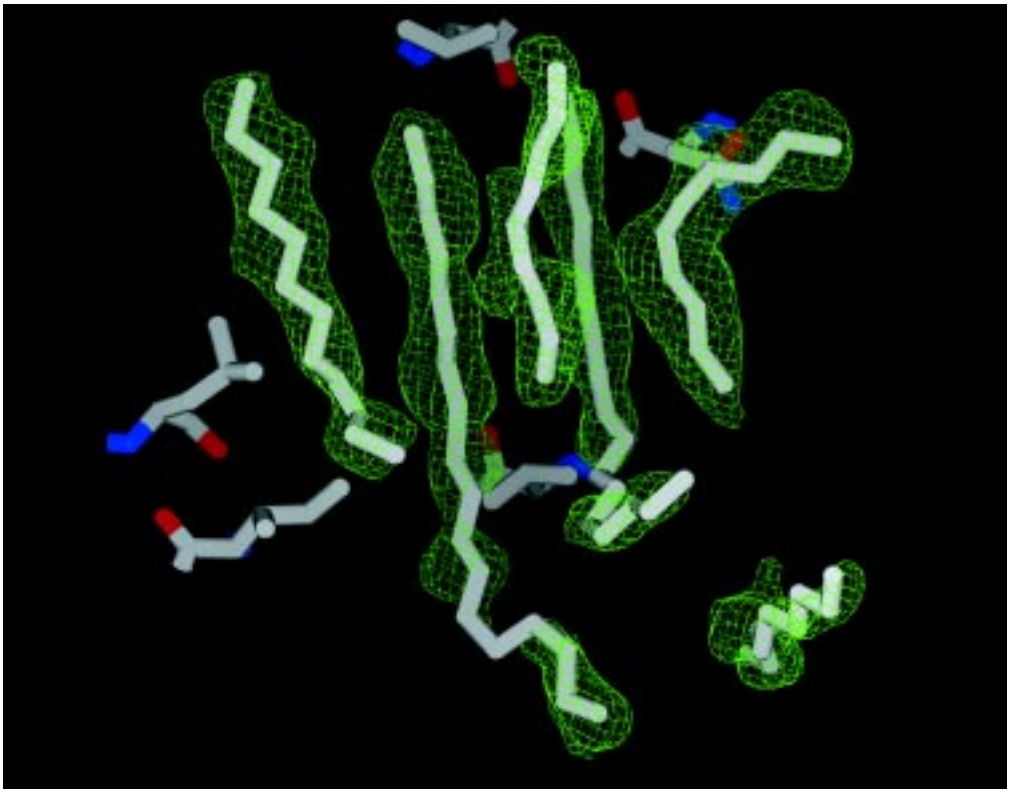
"No, we don't expect much attention," sighed Chong Hwan Chang, a DuPont Pharmaceuticals scientist from Delaware. "I would note that most cities do send a reporter when we come to town."

"But this is such a specialized field, if we can't excite the public, we do excite each other, "said Ronald Hamlin, president of an X-ray detector company. "We're actually quite happy being left in our little bubble."

The conference concludes tomorrow, still time for our city to give the crystallographers a big Minneapolis-sized send-off. But they'd rather we don't.

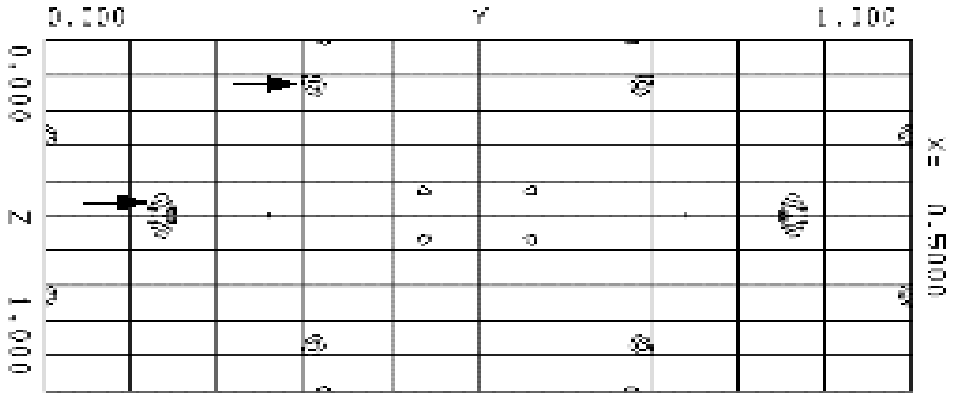
"The governor of Texas once declared a 'Crystallographer's Day,'" said Michigan State scientist Donald Ward. "We found that somewhat embarrassing."

(Reprinted with permission from the St. Paul Pioneer Press.)

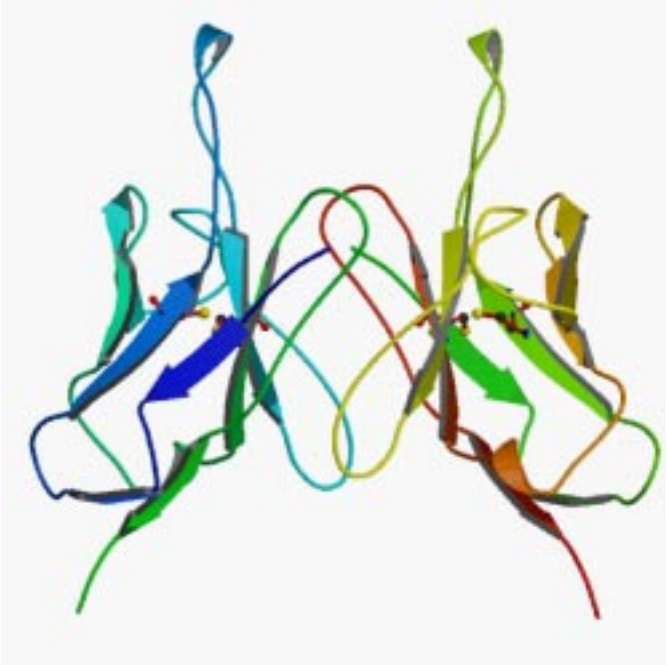


Ordered lipid electron density along the walls of the binding cavity in lipovitellin. Density observed at 100°K. From the Oxford Prize winning poster, P222, *Cryocrystallographic Structure of Lipovitellin Reveals Bound Lipid Molecules within the Major Cavity*.
James R. Thompson and Leonard J. Banaszak.

Vendors and posters were in the exhibition hall at the RiverCentre



Above, a 4 Å resolution anomalous difference Patterson map showing the Harker vectors of the disulfide bonds in the Len protein.



Right, ribbon drawing structure of Len protein determined from a sulfur single-wavelength anomalous scattering shasing method. (The sulfur atoms corresponding to the Patterson peaks are colored as yellow spheres.)
From a Pauling Prize winning poster, P033, Low Resolution Sulfur “Super Atom” SAS Phasing of Macro-molecules Containing Disulfide Bonds. Chun-Jung Chen, John P. Rose, Gerold Rosenbaum, Bi-Cheng Wang.

Left, Speakers in the Transaction S1ymposium "Using Crystallography to Understand Enzyme Mechanism". (left to right) Chen Mao, Doug Ohlendorf, Nancy Horton, Charles Carter, Jr., Osnat Herzberg, David Christianson and Dagmar Ringe

2000 ACA Summer Course in X-ray Crystallography

Back row (left to right): G. Potikyan (Armenia), A.R. Tapia-Benavides (Mexico), V. Nastopoulos (Greece), B. Barata (Portugal), A. Visnjevac (Croatia), O. Lauenstein (Germany), P. Kursula (Finland); Front Row (left to right): K. Al-Mughrabi (Jordan), J.-Y. Ahn (Korea), A. Teodora (Portugal), E. Freire (Argentina), R.-L. Susana (Mexico, H. Hallak (Palestine), P. Le Magueres (France), K. Petersson (Sweden)

The 9th annual ACA Summer Course in Crystallography was held at the Georgia Center for Continuing Education on the Univ. of Georgia campus from July 7th to 19th, 2000. Of the 44 students, 30 came from 15 states in the US. The 14 remaining students formed a sizeable international group with students hailing from Armenia, Argentina, Croatia, Finland, Germany, Greece, Israel, Jordan, Korea, Mexico, Portugal and Sweden.

Morning sessions were devoted to lectures about the theory and practice of crystallography and X-ray diffraction. In the afternoons, students gained hands-on experience with crystal growth, mounting and data collection techniques involved in both small molecule and macromolecular crystallography. Lectures and/or discussions on advanced or special topics were held in the evenings.

Students and instructors of the macromolecular crystallography group.

During the 7 days of the small molecule portion of the course, students had the opportunity to work on numerous structural problems using previously measured data. Some students brought their own crystals for data collection. In all, about 14 new data sets were measured and analyzed successfully. One badly twinned sample was successfully resolved and the structure determined during the lab sessions, an exciting event for all involved.

Students and instructors of the small molecule crystallography group.

There were 24 course lecturers and laboratory tutors contributing to the success of this year's Summer Course. Lecturers for the small molecule/ fundamentals portion of the course were: Wally Cordes (Univ.of Arkansas), Bryan M. Craven (Indiana Univ. of Pennsylvania), Steve Geib (Univ. of Pittsburgh), Herbert Hauptman (Hauptman-Woodward Inst.), Richard Marsh (California Inst. of Technology), Gary Newton (UGA), Ward Robinson (Canterbury Univ., New Zealand), John P. Rose (UGA), Robert A. Sparks (Bruker AXS consultant) and Bi-Cheng Wang (UGA). Macromolecular lecturers were: Andrzej Joachimiak (APS/SBC-CAT), Zhi-Jie Liu (UGA), Cory Momany (UGA), Gary Newton (UGA), John P. Rose (UGA), Robert Sweet (Brookhaven National Laboratory), Bi-Cheng Wang (UGA), Charles Weeks (Hauptman-Woodward Inst.). We were also very delighted to have Professor Ken Hardcastle (Emory Univ.) participate on an ad-hoc basis.

Several lecturers also participated in the laboratory sessions. Principal tutors and assistants in the small molecule laboratory sessions were: Bruker - Charles Campana (Bruker AXS), Ward Robinson and Steve Geib; Molecular Structure Corp. - Thomas Concolino (MSC), Kris Tesh (MSC) and John P. Rose; Nonius - Dan Frankel (Nonius, Inc. USA) and Doo Won Lee (Georgia State Univ.)

Macromolecular laboratory and workshop sessions were directed by Chun-Jung Chen, Stephen Foundling (Bruker AXS), Zhi-Jie Liu, Gary Newton, John P. Rose, Bram Schierbeek (Nonius, Inc., Delft, The Netherlands) and Bi-Cheng Wang. We are also grateful for the help provided by Dr. Wolfram Temple, UGA graduate students Lu Deng, Peter Horanyi, Florian Schobot, Vasundara Srinivasan, Zhaojie Wang and laboratory staff members Lily Li, Dan Rose and Andrew Wang.

The ACA Summer Course is again very grateful for the generous support of the ACA, IUCr, The Univ. of Georgia, Bruker AXS, Douglas Instruments, Emerald Biostructures, Hampton Research, Molecular Structure Corp. and Nonius, Inc.

The 10th annual ACA Summer Course in X-ray Crystallography is scheduled for June 8-20, 2001 at the University of Georgia. Check web page at http://BCL15.bmb.uga.edu/aca2001.html for the most recent information.

Gary Newton

The Sealy Center Structural Biology Symposium

This year's symposium, held in Galveston, TX, May 19-21, 2000, and chaired by Wayne Bolen and Jim Lee, had three focal points: protein folding and aggregation, enzyme regulation as a basis for drug design, and novel methods for studying the structure of biomolecules. As always, speakers at the meeting presented striking new findings at the interface between structural biology and medicine.

Mad cows and β - sheets

The first of these was introduced by Kurt Wüthrich (E.T.H., Zurich Switzerland), in the keynote speech, who showed structures of the normal cellular forms of prion proteins determined by NMR spectroscopy. The prion protein, a normal cell protein, was originally isolated in an aggregated form from the brains of animals suffering from scrapies. More recently, outbreaks of other transmissable spongiform encephalopathies (TSE) in animals and man ("Mad Cow Disease" and a new variant of Creutzfeldt-Jakob Syndrome) have emphasized the need to understand the causative agent of these diseases and derive methods to prevent their spread. The recombinant form of the Prion protein has a flexible, unstructured N-terminal tail of 100 residues, attached to a globular C-terminus containing three long helices and a very short anti-parallel β-sheet. Other groups have suggested that the toxicity of the aggregated protein can be attributed to formation of an extended b-sheet conformation, based on FTIR spectra.

Previously, only brain extracts from infected animals or humans could induce TSEs, although mice expressing mutant forms of the human prion protein associated with diseases developed plaques in the brain and died earlier than control mice. Fred Cohen (UCSF) presented recent experiments that use purified proteins. "Mini-prions", segments of the prion protein, accelerated death when injected into the brains of transgenic mice producing the appropriate prion protein. A chemically produced 55 residue peptide, from region 90-144 (part of the unstructured region and the first β-strand), if in a "β" conformation, reduced the lifetime of transgenic mice carrying the human prion protein with a P101L mutation to 360 days. Transgenic mice that were not infected or injected with the same peptide that had not been aggregated in organic solvent live ~600days. To test whether the synthetic peptide started a serially transmissible decay process, brain extracts derived from the animals in the first study were inoculated into a fresh cohort of transgenic mice. Those injected with the brains of

Left to right, Enrico Gratton, Lila Gierasch, Wayne Bolen, Kurt Wüthrich, Vince Hilser, Catherine Schein, Werner Braun

Wah Chiu and Kighake Soman

mice that received the aggregated peptide died at 360 days with neuropathology diagnostic for a prion disease. The control mice are still alive (the experiment is technically not finished yet), but Fred is still not anxious to announce he has the first infectious prion not isolated from brain tissue. As some of the transgenic mice spontaneously develop neurological symptoms and die prematurely, the peptide may have just accelerated a process that was eventually going to kill the mice. His group is also using a neuroblastoma cell assay to search for substances that inhibit the formation of the prion aggregates.

Lila Gierasch (U. Mass Amherst) discussed some of the ways the β-sheets in normal proteins are stabilized, based on her results with members of the cellular retinoic acid binding protein family (CRABPI). This protein has a clam like shape, where the retinoic acid is sandwiched between two β-sheets joined by a hinge region. Multiple sequence alignments indicated that absolutely conserved residues are predominantly in the helical regions, with a few clustered in the hinge region at the start of the β-sheets. As the residues specifying β-sheet formation are less stringently controlled, they looked at whether the types of interactions between side chains throughout the sheet structure were conserved. They found a spider web of long range hydrophobic interactions throughout the β-sheet region and a cluster of polar interactions in the hinge region between the sheets. She proposes that topology forms first, with the hydrogen bonds in the β-sheet forming at a later step in the folding. Her group is now working to trap folding intermediates, to find how they avoid aggregation.

Drugs that regulate enzyme activities

David Christianson (U. Pennsylvania) discussed how inhibitors of arginase might be useful counterparts to Viagra in regulating erectile function. Viagra sustains cellular levels of cyclic-GMP by inhibiting phosphodiesterase V, which sustains smooth muscle relaxation. Cyclic-GMP synthesis is triggered by nitric oxide (NO), which is generated by NO synthase. The metalloenzyme arginase lowers the activity of NO-synthases in penile tissues by competing for their common substrate, arginine. An arginase inhibitor should not only work earlier in the pathway that generates NO, but should also be more specific. Using the crystal structure of arginase, his group designed a series of ω-borono-α- amino acids specific for the active site of arginase that did not inhibit NO-synthases. One of these induced smooth muscle relaxation in organ bath experiments with rabbit and human penile tissue.

John Olson (Rice) discussed redesigning recombinant hemoglobin (rHb)to make novel oxygen delivery pharmaceuticals. Whole blood cannot be stored for emergency use for long periods of time, even with refrigeration. For use as a blood substitute, rHb must have moderate O_2 affinity (P_{50}=20-40 mM), discriminate against CO, rapidly bind and release O_2, and resist oxidation, heme dissociation, and denaturation . The kidney clears free Hb dimers and often converts them to toxic degradation products. Cross-linked Hb tetramers, generated chemically from animal blood isolates or produced with linkers in bacteria, have solved the dissociation problem. However, the free Hb tetramer itself is toxic due to scavenging of NO and interference with blood pressure regulation. Using myoglobin as a model, Olson's group pinpointed mutations of several residues around the heme-binding site that would make the internal binding cavity too small for rapid reaction with NO, while still allowing rapid release of oxygen. The next goal of this collaborative project (with Baxter Hemoglobin Therapeutics) is to produce stabilized rHb in bacteria for $5-8/gram.

Brian Sykes (U. Alberta) uses NMR to analyze the differences between the skeletal and cardiac forms of the calcium regulatory protein Troponin C (TnC). The N terminal end of the skeletal form "opens up" as Ca binds, inducing a succession of protein-protein interactions that lead the muscle to contract. However, Ca induces smaller changes in the cardiac form. Instead, cardiac troponin inhibitor (TnI) is needed to open up the molecule by binding to a hydrophobic area on the surface. An isolated peptide from this inhibitor formed a stable helical structure, characterized by a very hydrophobic surface. Adding a cardiac function inhibitor could prevent this interaction *in vitro*, suggesting that the mechanism could be used to design further cardiac active drugs.

Xiaodong Cheng (UTMB) presented another example of structural regulation of the activities of proteins, in this case comparing the two isoforms of cAMP dependent protein kinase (PKA). Protein footprinting and site directed mutagenesis were used to pinpoint two residues that differentially control the response of type I PKA, which is associated with cell proliferation, and type II PKA, associated with growth arrest states, to inhibitors.

Advances in structure determination

Joachim Frank (HHMI, Wadsworth Center, Albany NY) demonstrated the advantages of cryo-electron microscopy of single particles in determining the structure of the ribosome, and how it changes during translation. As the ribosomes on the grid surface are in a hydrated state, without staining, the structure is preserved in a close-to-native state. In principle, the method allows the use of time-resolved techniques, since reactive molecules can be added immediately before freezing. The binding of ligands such as tRNA and elongation factors (EF-G) to the ribosome can be visualized by cryo-EM and 3-D reconstruction. Even the relatively"low" resolution of the present method allows one to detect major changes that occur upon binding of EF-G. Movies provided a dynamic illustration of how the ribosomal subunits move as EF-G binds to the ribosome. The whole decoding center moves by as much as 10 Å in the process, and changes in overall structure of the ribosome occur up to 100 Å away from the decoding center. Dr. Frank's group was also able to separate the RNA and protein regions of the ribosome. The results indicate that no protein is involved in the catalytic activities of the peptidyltransferase center.

Kurt Wüthrich showed how newly developed NMR techniques may be the key for determining the structure of membrane proteins in micelle environments. Although a large molecular complex has a slow rotation rate, optimized TROSY (transverse

David Christianson, Werner Braun, and Wayne Bolen (left to right)

relaxation rotational spectroscopy) spectra of the *E. coli* membrane protein OmpX in DHPC micelles have very well defined peaks. These techniques allowed his group to determine the sequential assignments for this protein in about 1 month of work.

A new member of the UTMB faculty, Ehud Landau showed that lipidic cubic phases are an alternate concept for the crystallization of integral membrane proteins. Crystals of bacteriorhodopsin in monoolein1-monooleoyl-rac-glycerol (C18:1 cis-9) diffract to 1.9 Å resolution. Further, the protein is in a functional environment in the crystal, as light induces the photocycle. He was able, in collaboration with groups in Basel, Grenoble, and Uppsala, via cryotrapping, to determine the X-ray structure of early intermediates in the photocycle. Individual crystals were illuminated at 532 nm with a laser and their spectroscopic state determined with a microspectrophotometer. A difference electron density map of the ground to excited state revealed changes clustered around the retinal, particularly in the side chain orientations of K216, D212, D85 and the location of a key water molecule. The high resolution of the structures allowed them to see the retinal backbone move from all-trans to 13-cis.

Enrico Gratton (U. Illinois Urbana) introduced a new tool for sorting molecules by size and brightness in the cellular environment: fluorescence two-photon excitation and fluctuation spectroscopy. In normal spectroscopic modes, one obtains an average spectrum over a population of molecules. To obtain data about the heterogeneity of the population, one must extract components from this average. The highly sensitive detectors and precise laser sources now available allow one to do optical spectroscopy on a small volume of highly dilute macromolecules. Instead of an averaged signal, one obtains signal fluctuations that can be related to the specific characteristics of the individual molecules in the sample. A major advantage of two-photon excitation is that by using a near-infrared energy beam (the excitation wavelength for a variety of dyes is 800 nm), one can clearly separate the fluorescence emission spectrum from overlap with the exciting wavelength spread and eliminate Raman scattering from the solvent. Using a photon detector and a recorder, they were able to directly measure the diffusion rate and brightness of green fluorescence protein in cells. The many applications of the technique include direct measurement of complex formation and protein aggregation in cells.

Bruce Luxon (UTMB) discussed methods to analyze the dynamic interactions between proteins and DNA in regulatory complexes. Protein/DNA interactions are the basis of cellular control mechanisms. Dynamic simulations can be used to study these interactions and their stability in the presence of other competing processes in the cellular environment.

A genomic approach to structure

On Sunday morning, Marvin Cassman (NIGMS) brought the symposium back to a topic raised by Kurt Wüthrich, in his keynote address: the need for more rapid determination of protein structures. However, the major concern at the NIGMS presently is how to get scientists from many different backgrounds to work together to analyze complex systems, whose "behaviour is determined by combinations of multiple interacting components whose quantitative expression may vary in time and space". He used the EGF signal transduction pathway as an example, noting that this was truly not a pathway but a network. Biologists, he said, must stop thinking in two

dimensional wiring diagrams without space and time dimensions. A new form of scientific culture is emerging. Unlike the traditional “hunter gatherer”, the scientific “harvester” works in large, highly collaborative groups in a data rich environment, with advanced tools appropriate for analysis of large bodies of data. The preferred mode of data transmission is likely to be through databases rather than, or in addition to, publications. To further such efforts, the NIGMS has established a variety of consortium awards (glue grants); furthered access to databases and large facilities, such as synchrotrons, high resolution electron microscopy centers, and high-field NMR; and developed programs, including structural genomics, that involve high-throughput data production by large collaborative teams.

The symposium organizers deserve a warm recognition for achieving, for the 5th year in a row, a perfect harvester environment at the meeting.

Poster prizes

For the second year, prizes were awarded for posters presented by graduate students and post-docs. The 1st prize ($500) was awarded to Andrea Bertolotti-Ciarlet (Baylor, Houston) for "*Structural Requirements for Norwalk Virus Assembly*". Second ($300) and third ($150) prizes went to Leslie Hall (UT, San Antonio) for "*Dimerization of Lys7-SOD Association and Copper Delivery*" and Mathew Fesinmeyer (U. Washington) for "*TimeScales for Peptide Secondary and Tertiary Structure Formation*". Honorable mention went to Jennifer Stine (UT-San Antonio) for "*The Crystal Structure of Cucumber Stellacyanin*", HW Yang (UTMB) for "*The Design of High-Affinity Miniprotein Ligands*", and Kizhake Soman (UTMB) for "*Calculation of Protein Structures From A Minimum Number Of Constraints*".

Catherine H. Schein

Andrea Bertolotti-Ciarlet (Poster 1st Prize) and Werner Braun

The posters were well attended.

Left to right. Wayne Bolen, Lila Gierasch, Brad Thompson, Marvin Cassman, Fred Cohen, Bob Fox

ACA '01 - July 21-26, 2001 Los Angeles, California

Preliminary Program

Saturday July 21
- Workshops (Tentative)
  - ISAS Phasing Method
  - Real Space Pair-wise Distribution Functions
- Opening Reception - LA Central Library

Sunday July 22
- Hot New Structures
- Gas Clathrates, Ices and Planetary Materials
- Material Sciences
- Small Angle Scattering
- Computational Methods and Analysis
- Posters
- YSSIG Mentor/Mentee Dinner

Monday, July 23
- High-throughput Crystallography
- Methodology
- General Interest
- Amorphous Materials
- Structural Genomics Projects
- Small Molecules
- Posters
- YSSIG Mixer

Tuesday, July 24
- Complexes/Large Molecules
- Service Crystallography
- Membrane Proteins
- Synchrotron Radiation
- Amorphous Materials
- Posters
- Evening Lecture - Planetary Ices

Wednesday, July 25
- Hot New Methods
- Small Molecules
- Fiber Diffraction
- Problem/Difficult Structures
- Banquet - Biltmore Hotel

Thursday, July 26
- General Interest
- Signal Transduction
- Getty Center Trip

The Program is still in the planning stages and is subject to change.

Local Information

http://www.hwi.buffalo.edu/ACA/ACA-Annual/LosAngeles/LosAngeles.html

The currently planned social events for ACA2001 are all in spectacular settings. We will meet in the Downtown Los Angeles Financial District, full of gleaming modern structures, very well-preserved older buildings, and public art. Even our meeting hotel, the Westin Bonaventure, is pretty impressive and is something of a Los Angeles icon (John Portman and Associates, architects; 1974-1976). Several movies were at least in part filmed there (In the Line of Fire, etc.). It has a restaurant and a rotating bar on top. The opening reception is planned for the Los Angeles Central Library, a mid-twenties deco structure (Bertram Goodhue, architect), since renovated, updated, expanded and ornamented. We are planning another reception at the Museum of Contemporary Art (Arata Isozaki, architect; features the "Monroe Curve"). The annual banquet will be at the historic Regal Biltmore Hotel (Italianate Beaux Arts 1922-1923 by Schultze and Weaver; recently renovated). The Biltmore was used as setting for several movies, including Chinatown, Ghostbusters, The Sting, The Fabulous Baker Boys, and Vertigo, among others. Its history goes on for pages. Those of you arriving early may see movie crews working in the streets of Downtown. The newly completed Metro system can quickly take you into Hollywood, and a new express bus line can quickly take you as far as Santa Monica Beach for minimal expense. For those of you staying through the end of the meeting, we plan an excursion to the awesome (and blindingly bright) Getty Center (Richard Meier; gardens by Robert Irwin), on a hill overlooking Los Angeles.

Daniel Anderson, Local Chair

Duncan McRee (Program Chair, dem@scripps.edu),
Kathy Kantardjieff (Local Chair, kkantardjieff@fullerton.edu),
and Dan Anderson (Local Chair, dha@mbi.ucla.edu)

Academia-Industry Outreach Workshop and The Industrial Physics Forum

When:
WORKSHOP: November 5, 2000
FORUM: November 6-7, 2000
(with opening reception and dinner Sunday evening, Nov. 5)

Where:
San Diego, California (at the Hyatt Islandia, with Monday banquet at the Birch Aquarium)

Why:

To learn about industrial applications of physics from the perspective of one of the world's leaders in commercializing applications of fission and fusion.

To spend three days interacting with leaders in industrial physics.

To stimulate interaction between academia and industry.

To learn about the technical and workforce needs of industry so that you can mentor your students about opportunities in the private sector.

To expand your perspective on the potential industrial applications of your research.

To promote novel programmatic ideas for department revitalization.

The WORKSHOP is designed to be an interactive meeting focused on stimulating relationships between academic and industrial physicists, sponsored by AIPCorporate Associates, Project Kaleidoscope, the Society of Physics Students, the APS Committee on Careers and Professional Development, and the National Task Force on Undergraduate Physics:

The Workshop will consist of three sessions, each consisting of a panel and subsequent breakouts:

1) Listening to industry: Insider perspectives on meeting industry's workforce and technical needs.
2) Making connections / forming partnerships: Insights and ideas from those who have succeeded.
3) Taking action: Professional masters degree programs in physics.

The theme of the Forum is Physics, Energy, and Defense: Synergistic Interactions, hosted by General Atomics in conjunction with the APS Forum on Industrial and Applied Physics:

Advanced physics is a key tool for energy and defense research. The meeting will explore the interactions between research in physics and advances in energy and defense technologies, using the example of R&D performed at General Atomics. For example, the program includes talks on:
Physics, Energy, and Defense in the 21st Century
Controlled Fusion
Acceleration: From Particles to Aircraft
Turning Physics into Technology
The Defense R&D Workforce
Addressing Public Concerns about Energy and Nuclear Power R&D
Underwater Ocean Acoustics
LIGO
The Small World Problem in Networking
The Intersection Between Biochemistry and Materials Science

A common feature of the Industrial Physics Forum is the tour of the host's facilities. This year, you will tour:
General Atomics' National Fusion Research Facility
GA Aeronautical Systems, Inc. Unmanned Aeronautical Vehicle facility.

THINK ABOUT IT:

As a physicist, you may be challenged to forge a research program that is fundable by one of the federal science funding agencies. Such a program must meet national needs. If you are interested in one perspective on how physics research serves national needs, this meeting is for you.

As a teacher and mentor, you will be called upon to guide students on their professional options as a physicist. National laboratories and industry provide more opportunities for physicists than academia, at all degree levels. If you want to provide your students with timely information about the technical and workforce needs of industry, this meeting is for you.

As an industrial physicist, you need access to recent discoveries and to qualified scientists and technical workers. If you want to forge relationships with academic physicists who are on the cutting edge of research and who are training your future employees, this meeting is for you.

For complete program information for the Workshop and Forum, and to register online, go to:

http://www.aip.org/aip/corporate/general/meeting.html

For more information, contact Liz Dart at Ldart@aip.org or 301-209-3034

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www.fujimed.com

Gilson Inc. Cyberlab
www.gilson.com

Hampton Research
www.hamptonresearch.com

International Centre for Diffraction Data
www.icdd.com

J Schneider Electrotechnik GmbH
j.schneider-elektrotechnik@t-online.de

MAR USA, Inc.
www.mar-usa.com

Microsource
www.bede.com/micro.html

Molecular Structure Corp.
www.msc.com

Nonius Company
www.nonius.com

Osmic, Inc.
www.osmic.com

Oxford Instruments Inc.
www.oxford-instruments.com

Protein Data Bank
www.rcsb.org/pdb

Protein Solutions, Inc.
www.protein-solutions.com

Roper Scientific
Trenton, New Jersey

UOV/Biblioteca Universitaria - Oviedo, Spain
Oviedo, Spain

X-Ray Research Gmblt
www.marresearch.com

Sulfate Minerals

A short course on "Sulfate Minerals - Crystallography, Geochemistry, and Environmental Significance" will take place November 11-12, 2000 in Tahoe City, California, USA. This short course, sponsored by the Mineralogical Society of America, will review the crystal chemistry of sulfate minerals and provides an overview of the most important settings of sulfate mineral formation, including hydrothermal systems, ground-water systems, evaporites, and weathering environments, both acidic and alkaline. The spectroscopy of sulfate in earth materials will be covered, including solid phases, the aqueous phase, and the mineral-water interface. Thermodynamics of sulfate minerals will be the basis of several presentations, including a summary of available thermodynamic properties for end-member sulfate minerals and a discussion of binary solid solutions and their interactions with aqueous solutions. Other topics will include geochemical modeling, metal-sulfate salts from sulfide oxidation, the alunite-jarosite supergroup, stable isotopes, and radiometric dating. For information on registration and a list of speakers see http://www.minsocam.org/MSA/SC_SO4.html. Related topical sessions on sulfate minerals in hydrothermal systems and low-temperature environments will be held at the 2000 annual meeting of the Geological Society of America, in Reno, NV, USA, on Nov. 13-16, 2000. For more information, see http://www.geosociety.org/meetings/200/t-top4.htm.

Charlie Alpers

Meeting Calendar

In order to conserve space and paper, contact points for most meetings announced in previous newsletter issues will not be repeated. More complete information can be found in back issues of the newsletter.

OCTOBER 2000

11-15 10th International Symposium on Small Particles and Inorganic Clusters (ISSPIC), Atlanta, GA More information can be found at http://www.physics.gatech.edu/isspic10/

26-28 Pittsburgh Diffraction Conference, Pittsburgh, PA. Contacts: Bryan Craven, President. Chemistry Dept., IUP. 1491 Donahue Road, Creekside, PA 15732. (724)-397-9211. alpacone @mail.microserve.net. Brian Burkhart, President-elect. brian.burkhart@milliken.com.

NOVEMBER 2000

11-12 Sulfate Minerals - Crystallography, Geochemistry, and Environmental Significance (MSA short course), Tahoe city, CA More information can be found at http://www.minsocam.org/MSA/SC_SSO4.html.

JUNE 2001

8-20, 2001ACA Summer Course in Crystallography, Athens, GA. Georgia Center for Continuing Education University of Georgia, http://BCL15.bmb.uga.edu/aca2k.html

JULY 2001

21-26 ACA '01 Los Angeles, CA. Local Chairs: Katherine Kantardjieff (CSU-Fullerton, kkantardjieff@exchange.fullterton.edu) and Dan Anderson (UCLA, dha@mbi.ucla.edu). Program Chair: Duncan McRee (Scripps, dem@scripps.edu). Meeting website: www.hwi.buffalo.edu/ACA/ACA-Annual/LosAngeles/

MAY 2002

25-30 ACA '02 San Antonio, TX. Local Chairs: Ray Davis (UT Austin) and Marv Hackert (UT Austin, m.hackert@mail.utexas.edu). Program Chair: Wally Cordes (Arkansas, wcordes.comp.uark.edu).

AUGUST 2002

6-15 19th IUCr General Assembly and Intl. Congress of Crystallography. Jerusalem, Israel. Contact:J. Bernstein, Ben Gurion University, Beer Sheva, Israel.

Contributors to This Issue

Cele Abad-Zapatero, Andrew Allen, Charlie Alpers, Leonard J. Banaszak, Herb Bernstein, Joel Bernstein, Laura Billings, Jim Britten, Carol Brock, I. David Brown, Chun-Jung Chen, Connie Chidester, Patti Coley, Bill Duax, Marcia Evans, Barry Farmer, Judy Flippen-Anderson, Tom Furnas, Keith Hodgson, Wim Hol, John Huffman, Bruce Jacobson, Dan Kirschner, Helen M. McDonnell, Gary Newton, Doug Ohlendorf, Thomas Rieker, John P. Rose, Gerold Rosenbaum, Catherine Schein, Clara Brink Shoemaker, Bill Stallings, Ron Stenkamp, David Templeton, James R. Thompson, Brian Toby, Bi-Cheng Wang, Shin Whanchul, Cynthia Wolberger, Cho Sang Woo.

Positions Available

It is expected that the employers listed in this publication are equal opportunity employers who wish to receive applications from qualified persons regardless of age, national origin, race, religion, sex or physical handicaps. Please inform the Editor when the positions are filled, and of any positions that do not give opportunities to all applicants. Ads will appear in two successive newsletters unless the Editor is notified that the advertisement should be continued longer or discontinued earlier.

For the most up-to-date listings check the ACA Home Page under the Positions Vacant heading.

http://www.hwi.buffalo.edu/ACA/

Positions Previously Listed

Macromolecular Crystallographer

Pharmacia has an opening for a Research Scientist in the Macromolecular Crystallography Group at Kalamazoo, Michigan. The strong candidate will have a Ph.D. in Chemistry, Biochemistry or related field with extensive research laboratory experience and a strong record of success in crystallographic structure determination. Apply as indicated in the next ad referring to position #900913

Crystallization Biochemist, BS/MS

The successful candidate will work as a member of the macromolecular crystallography laboratory. Responsibilities include the preparation of proteins and ligand complexes for crystallization experiments. For confidential consideration apply on-line at www.pharmacia.com (hyperlink to Pharmacia and Upjohn, Employment Opportunities) or send your resume and a description of your research experience to: Dr. Eric T. Baldwin, Structural, Analytical and Medicinal Chemistry, 7255-209-102; Pharmacia; 301 Henrietta Street; Kalamazoo, MI, 49007, USA. E-mail: eric.t.baldwin@am.pnu.com. Refer to position #900087

Francis Eppes Scholar in Macromolecular X-ray Crystallography

The Structural Biology program of Florida State University is seeking a distinguished macromolecular X-ray crystallographer to fill an endowed chair position. The Structural Biology Program at FSU consists of eleven core faculty -four in macromolecular X-ray crystallography, three in NMR, two in EPR spectroscopy, one in cryo-EM and one in mass spectroscopy. Nominations or applications (with letter of application, curriculum vitae and list of three potential referees) should be sent to: Dr. W. Ross Ellington, Eppes Scholar Search Committee, Department of Biological Science, Florida State University, Tallahassee, FL 32306-4370